Original Article

Causal relationship between serum metalloproteinase 12 levels and aortic dissection and aortic aneurysm: a bidirectional Mendelian randomization study

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Background: Elevated matrix metalloproteinase-12 (MMP-12) levels have been shown to be elevated in patients with aortic dissection (AD) and aortic aneurysm (AA). However, whether MMP-12 is associated with AD and AA has not been conclusively examined. The aim of this study was to clarify the role of MMP-12 in AD and AA formation and to verify the correlation between MMP-12 and AD and AA development at the gene level via Mendelian randomization (MR) analysis.

Methods: The data for analyzing MMP-12 gene mutations were obtained from the Integrative Epidemiology Unit (IEU) OpenGWAS database, which includes data from 21,758 European residents. Data on the genetic variation of AD and AA were retrieved from the FinnGen database. In the forward MR analysis, we evaluated the causal effect of MMP-12 on AD and AA. Subsequently, the causal association of AD and AA with MMP-12 was investigated in the reverse MR study. The inverse-variance weighting (IVW) method was the principal statistical technique used in this study.

Results: In the forward MR analysis, the IVW results showed that serum MMP-12 levels were positively related to an increased risk of AD [odds ratio (OR) =1.301; 95% confidence interval (CI): 1.002–1.697; P=0.048] and AA (OR =1.121; 95% CI: 1.007–1.248; P=0.04). For the reverse MR studies, no genetic relationships were observed between AD or AA and MMP-12 levels, nor was any heterogeneity or pleiotropy.

Conclusions: There was a correlation between serum MMP-12 and the risk of AD and AA. MMP-12 may be a potential therapeutic target for AD and AA.

Keywords: Matrix metalloproteinase-12 (MMP-12); aortic dissection (AD); aortic aneurysm (AA); Mendelian randomization (MR)

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Introduction

Aortic dissection (AD), an acute cardiovascular disease that can lead to sudden death, has a high rate of morbidity and mortality (1,2). Typical pathophysiological features of AD are characterized by the development of an aortic intimal tear and a false lumen between the intima and adventitia of the aorta wall, following blood entering the false lumen (3). AD can be divided into A and B types according to the site of intimal tear. The main treatment methods are surgical intervention (4), vascular intervention (5), and a hybrid approach (6). Despite significant improvement in the treatment of AD, in-hospital mortality remains high and the pathology is associated with major complications (7). Moreover, a proportion of patients may experience progression of the dissection during the follow-up and require re-operation (8). An aortic aneurysm (AA) is a pathological dilation of the aorta by more than 50% of the normal diameter of the aorta (9). Thoracic AA (TAA) is one of the most common AA types, with most of the cases occurring in older adults and male patients. A meta-analysis found that the total incidence of TAA is 5.3 million people/year, with an incidence of 0.16% (10), and its incidence has increased significantly in recent years (11). Similar to AD, AA is a serious threat to human health (12). At present, aortic computed tomography angiography was mainly used to evaluate aortic diseases in clinical practice. However, this examination only can evaluate the severity of current aortic diseases, and cannot reflect the progression of aortic diseases. A current study reported that blood biomarkers could be regarded as diagnostic biomarkers and prognostic biomarkers for chronic diseases (13). However, there were limited researches of biomarkers for predicting clinical aortic diseases. We hope to find suitable blood biomarkers to predict the progression of aortic diseases and provide reference for clinical and preventive work of aortic diseases.

Matrix metalloproteinase-12 (MMP-12), secreted mainly from macrophages, figures prominently in the regulation of extracellular matrix (ECM) decomposition and tissue remodeling (14). Research indicates that serum MMP-12 levels are connected with cardiovascular disease (15) and ischemic stroke (16). In one clinical study, MMP-12 levels were found to be significantly increased in abdominal AA tissues as compared with healthy aorta tissues (17). Another clinical study observed that elevated MMP-12 levels were present in both the aortic tissues and plasma of patients with AD (18). Furthermore, MMP-12 was reported to play a crucial role in the emergence of thoracic aneurysm and dissection (19), and MMP-12 deficiency was shown to attenuate aneurysm growth in mice (20). In the context of AD and AA, MMP-12 has been regarded as an outstanding biomarker for the incidence and progression of AA.

Despite the increasing number of studies showing that MMP is associated with AA, the conclusions of the current study do not provide a very firm and positive explanation.

The primary factors which included previous clinical studies always with small sample sizes, and the presence of confounding factors. In addition, observational studies tend to indicate the correlation, which may exist the potential reverse causality. Therefore, it is very necessary to conduct large-scale research to establish a definitive causal relationship between MMP and AA, further exploring their role as therapeutic targets in mitigating AD. Of course, the genetic association of MMP-12 with AD or AA remains unclear.

Mendelian randomization (MR) is an analytical method used for evaluating variable exposure or risk factors and clinical prognoses (21). Randomized controlled trials and observational studies cannot reliably determine causality due to the potential for confounding or reverse causality; however, MR is not subject to these pitfalls, as genetic variants affect outcomes only through exposure factors and are randomly allocated at conception (21,22). We present this article in accordance with the STROBE-MR reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-377/rc).

Highlight box

Key findings

- Mendelian randomization (MR) analysis provides genetic evidence for a link between serum matrix metalloproteinase-12 (MMP-12) level and the emergence of aortic dissection (AD) and aortic aneurysm (AA).

What is known and what is new?

- Previous research has indicated a relationship between serum MMP-12 level and AD and AA; however, a causal relationship between these factors has not been established.
- In this study, we used bidirectional MR analysis to determine the causal relationship between MMP-12 and AD and AA. Serum MMP-12 and the occurrence of AD or AA were found to be correlated to some extent.

What is the implication, and what should change now?

- MMP-12 may be a potential therapeutic target for AD and AA.

Methods

Study design

This study was designed as a bidirectional two-sample MR analysis. First, we examined the causal effects of serum/plasma of MMP-12 on AD and AA. Subsequently, the estimation of the causal effects of AD or AA on MMP-12 was conducted (*Figure 1*). Genetic variants were required to meet three rigorous criteria: (I) instrumental variables (IVs) were closely associated with exposed factors; (II) IVs were independent of the confounding factors that could influence exposure and outcome; and (III) IVs affected the outcome only via exposure. For the processing of palindromic SNPs, the main method is to discard those SNPs with palindromic structure. This is because palindromic sequences can cause confusion in genetic analysis, especially when trying to infer allele frequencies. According to the way the Harmonize software processes it, if a SNP has a palindromic structure and its allele frequency information no longer provides information about the chain, this will result in an inability to perform a valid genetic analysis. Therefore, we deleted the palindromic sequence before determining the IVs.

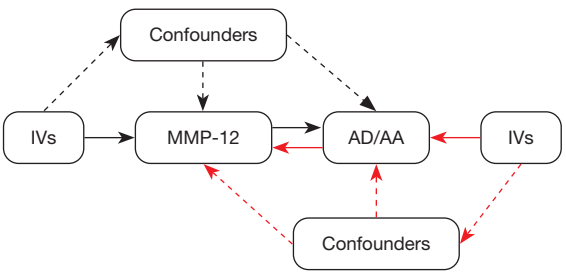

Figure 1 Study design of the bidirectional MR study on the association of serum MMP-12 levels with AD and AA. The black lines mean positive MR. The exposure is MMP-12 and the outcome is AD/AA. The red lines mean reverse MR. The exposures are AD/AA and the outcome is MMP-12. AA, aortic aneurysm; AD, aortic dissection; IV, instrumental variable; MMP-12, matrix metalloproteinase-12; MR, Mendelian randomization.

Data source and single-nucleotide polymorphism (SNP) selection of MMP-12

The genome-wide association study (GWAS) summary statistics for serum MMP-12 levels were obtained from the Integrative Epidemiology Unit (IEU) OpenGWAS project created by Folkersen *et al.* (23), which includes the data of 21,758 European individuals. The selection criteria IVs associated with MMP-12 in this MR analysis were as follows: (I) P values below 5×10^{-8}, which indicated that the IVs were significantly related to MMP-12 levels; and (II) the measured value of R^2 for linkage disequilibrium (LD) in the 10,000-kilobase window of 0.001. A total of seven SNPs (rs1144398, rs7126430, rs181951510, rs626750, rs12288698, rs117953762, and rs12975366) met the above requirements. In this study, the seven SNPs associated with MMP-12 were screened through platform PhenoScanner (Phenoscanner.medschl.cam.ac.uk). After rs12975366 was removed and palindrome sequences were excluded, only six SNPs were used for the MR study. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

Information and IV selection for AD and AA

Data for the SNPs related to AD and AA were obtained from the FinnGen project. The GWAS data on AD included 470 patients and 206,541 control individuals, with 16,380,411 SNPs (*Table 1*). In the initial search for proxy SNPs for AD, this threshold yielded only two potential IVs ($P<5\times10^{-8}$), and the limited SNPs will add increase the instability of the analysis results. We selected the genetic variants related to AD at $P<5\times10^{-6}$ as the IVs, with LD criteria of $r^2<0.001$ and 10,000 kb. Four SNPs (rs118055578, rs2302688, rs145146588, and rs36029774) that met the above conditions were examined in PhenoScanner V2 to

Table 1 Baseline characteristics of the MMP-12, AA, and AD datasets

Trait	IEU GWAS ID	Database	Population	Sample size	SNPs (n)
MMP-12	ebi-a-GCST90012070	NA	European	21,758	13,100,092
AD	finn-b-I9_AORTDIS	FinnGen	European	207,011	16,380,411
AA	finn-b-I9_AORTANEUR	FinnGen	European	209,366	16,380,417

AA, aortic aneurysm; AD, aortic dissection; GWAS, genome-wide association study; IEU, Integrative Epidemiology Unit; MMP-12, matrix metalloproteinase-12; NA, not available; SNP, single-nucleotide polymorphism.

exclude confounders. Finally, only three SNPs were used as IVs due to rs36029774 being related to height, which is a confounding factor for AD.

GWAS analysis on AA included 2,825 patients and 206,541 control individuals, comprising 16,380,417 SNPs. In the initial search for proxy SNPs for AA, this threshold yielded also only two potential IVs ($P<5\times10^{-8}$), and to facilitate the identification of additional SNPs, we relaxed the threshold to a more lenient value ($P<5\times10^{-6}$). But there were 21 SNPs for AA which we considered that the number of SNPs were an increase in the number level compared to AD ($P<5\times10^{-6}$ as the IVs for AD). Therefore, the cutoff values of independently associated SNPs were set as $P<5\times10^{-7}$, $r^2<0.001$, and 10,000 kb. After screening, five SNPs associated with AA were examined online with PhenoScanner, and palindromes were excluded. rs77097530 was removed due to its uneven palindrome sequence. Finally, only four SNPs (rs12406058, rs79958663, rs61914381, and rs9316871) were selected as IVs for AA.

Statistical analysis

In this bidirectional MR study, inverse-variance weighting (IVW) was selected as the primary means to determine the causality between exposure and outcome. First, in forward MR, we used two-sample MR analysis to estimate the causal effect of serum MMP-12 levels on AD and AA. Subsequently, the genetic associations of AD or AA on serum MMP-12 levels were calculated in the reverse MR study. We used the Cochran's *Q* statistic to quantify the heterogeneity among SNPs. When heterogeneity was present, the multiplicative random effect in IVW was adopted; otherwise, a fixed-effect model was used (24). The MR-Egger intercept test was conducted to assess multiple effects. The MR pleiotropy residual sum and outlier (MR-PRESSO) global test was used to search for outliers. Identified outliers were removed, and MR analysis was repeated. The leave-one-out method was used to evaluate the robustness of the outcomes.

All the analyses were performed in R version 4.2.1 (The R Project for Statistical Computing, Vienna, Austria). The R packages included "two-sample MR" and "MR-PRESSO" packages.

Results

The causal effects of MMP-12 levels on AD and AA

Ultimately, six SNPs were selected as IVs for serum MMP-12 levels according to the above-described setting conditions and testing procedures (Table S1). The *F* statistic was used to quantify the strength of the IVs, and the F values for each IV were greater than 10, indicating that our selected IVs were not affected by weak IVs.

We primarily selected the IVW-fixed-effect model to assess the causal effect of MMP-12 on AD and AA. The outcomes of the IVW method indicated that elevated serum MMP-12 levels are a risk factor for AD [odds ratio (OR) =1.301; 95% confidence interval (CI) 1.002–1.697; P=0.048] and AA (OR =1.121; 95% CI: 1.007–1.248; P=0.04). The clinical interpretation of our results showed that the risk of AD increased by 30.1% for each additional elevated serum standardized unit of MMP-12 level, and the risk of AA increased by 12.1% for each additional elevated serum standardized unit of MMP-12 level. The results of the other four methods of MR showed a similar tendency but did not reach statistical significance (*Figure 2*). It was worth noting that in our study, the borderline statistical significance (P values near 0.05) was observed in the IVW analysis results showed statistical significance between MMP-12 and the risk of AA (P=0.04) and AD (P=0.048), which leaded us to be more careful in interpreting and generalizing our results.

As shown in *Figure 2* based on the Cochran's *Q* test, heterogeneity was ruled out. MR-Egger intercept tests showed no horizontal pleiotropy. The MR-PRESSO analysis indicated no significant outliers for the included IVs that could influence the results. The scatter plots for the causal effect of MMP-12 are shown in *Figure 3*. The leave-one-out method indicated that the results would not be affected after removal of each SNP (Figure S1). The forest plots and funnel plots are shown in Figures S2,S3.

The causal effects of AD and AA on MMP-12 levels

According to the P value and LD agglutination method, three and four gene variants were selected as grade IV AD and AA, respectively (Tables S2,S3). The F statistic confirmed the strength of the selected IVs, and MR-PRESSO analysis revealed no obvious outliers. Based on the IVW-FE model, there was an increased risk of AA observed with elevated MMP-12 level (OR =1.033; 95% CI: 0.964–1.107; P=0.36), but there was no statistical significance. In addition, no genetic association was observed for AD (OR =1.013; 95% CI: 0.971–1.057; P=0.56) on MMP-12 levels in the IVW-FE model. Neither heterogeneity nor pleiotropy was observed in the reverse MR (*Figure 4*). Moreover, the results of leave-one-out method, forest plots, funnel plots, and scatter plots are provided in Figures S1-S4.

Exposure	Outcome	nSNPs	Method	P value	OR (95% CI)	Heterogeneity test P	MR-Egger intercept P	MR-PRESSO global test P
MMP-12	AD	6	MR-Egger	0.39	1.379 (0.715 to 2.661)	0.25	0.86	
		6	Weighted median	0.13	1.256 (0.933 to 1.691)			
		6	Inverse variance weighted	0.048	1.301 (1.002 to 1.697)	0.37		0.43 (raw, 0 outliers)
		6	Simple mode	0.68	1.120 (0.674 to 1.861)			
		6	Weighted mode	0.26	1.225 (0.896 to 1.675)			
MMP-12	AA	6	MR-Egger	0.25	1.180 (0.927 to 1.501)	0.65	0.67	
		6	Weighted median	0.10	1.105 (0.980 to 1.246)			
		6	Inverse variance weighted	0.04	1.121 (1.007 to 1.248)	0.75		0.79 (raw, 0 outliers)
		6	Simple mode	0.54	1.062 (0.890 to 1.273)			
		6	Weighted mode	0.20	1.101 (0.970 to 1.251)			

P<0.05 was considered statistically significant

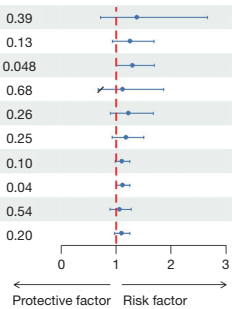

Figure 2 Associations of serum MMP-12 levels with AD and AA. MMP-12 was found to be a potential risk factor for AD and AA. AA, aortic aneurysm; AD, aortic dissection; CI, confidence interval; MMP-12, matrix metalloproteinase-12; MR, Mendelian randomization; nSNP, nonsynonymous single-nucleotide polymorphism; OR, odds ratio; PRESSO, pleiotropy residual sum and outlier.

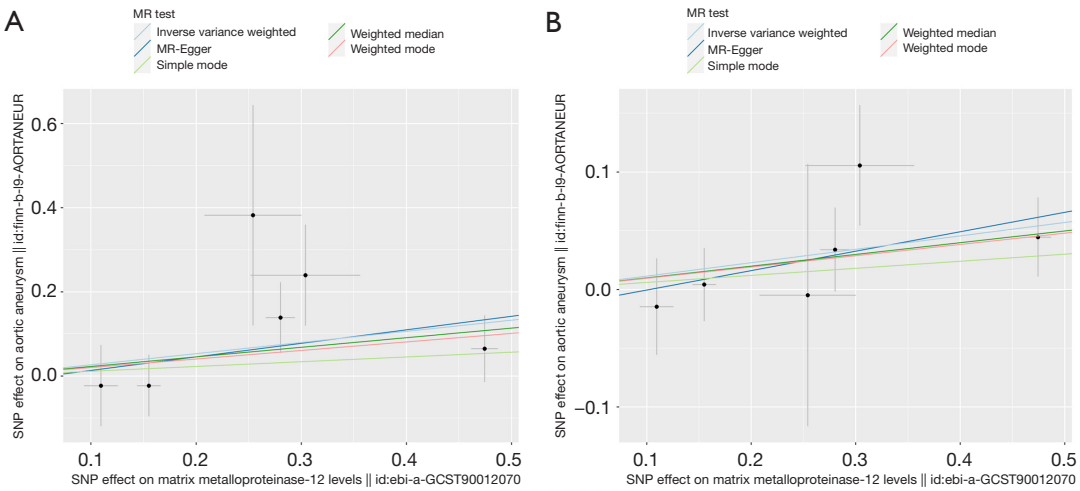

Figure 3 Scatter plots of the causal effect of MMP-12. (A) The scatter plot of the causal effect of MMP-12 on AD. (B) The scatter plot of the causal effect of MMP-12 on AA. AA, aortic aneurysm; AD, aortic dissection; MMP-12, matrix metalloproteinase-12; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

Exposure	Outcome	nSNPs	Method	P value	OR (95% CI)	Heterogeneity test P	MR-Egger intercept P	MR-PRESSO global test P
AD	MMP-12	3	MR-Egger	0.91	1.008 (0.910 to 1.116)	0.59	0.93	
		3	Weighted median	0.60	1.014 (0.964 to 1.066)			
		3	Inverse variance weighted	0.56	1.013 (0.971 to 1.057)	0.86		
		3	Simple mode	0.71	1.013 (0.957 to 1.072)			
		3	Weighted mode	0.64	1.016 (0.959 to 1.076)			
AA	MMP-12	4	MR-Egger	0.84	0.959 (0.667 to 1.379)	0.88	0.67	
		4	Weighted median	0.36	1.038 (0.959 to 1.123)			
		4	Inverse variance weighted	0.36	1.033 (0.964 to 1.107)	0.94		0.94 (raw, 0 outliers)
		4	Simple mode	0.88	1.010 (0.902 to 1.131)			
		4	Weighted mode	0.43	1.047 (0.949 to 1.155)			

P<0.05 was considered statistically significant

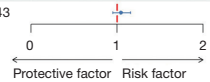

Figure 4 Causal effects of AD and AA on serum MMP-12 levels. No genetic associations were observed for AD or AA with serum MMP-12 levels. AA, aortic aneurysm; AD, aortic dissection; CI, confidence interval; MMP-12, matrix metalloproteinase-12; MR, Mendelian randomization; nSNP, nonsynonymous single-nucleotide polymorphism; OR, odds ratio; PRESSO, pleiotropy residual sum and outlier.

Discussion

In this bidirectional MR analysis study, we examined the genetic association between serum MMP-12 levels and AD and AA. Our study demonstrated that MMP-12 levels are causally related to an increased risk of AD and AA. Meanwhile, no causal effects of AD and AA on MMP-12 levels were observed in our study.

MMP-12 is a key immunofibrotic regulator secreted by macrophages, and it has been confirmed by more and more relevant studies that it can be a key marker of inflammation deterioration and fibrosis. MMP-12 can break down the ECM for tissue remodeling and repair, but excessive MMP-12 activity is associated with the occurrence and development of a variety of diseases. Several studies investigating the association of MMP-12 levels in AD and AA have been conducted. In an analysis of an Italian population including 23 patients with AD, increased blood MMP-12 levels were found in patients with Stanford-A acute AD (25). Similarly, MMP-12 level exhibited a significant rise in messenger RNA expression in human abdominal AA wall samples compared to nondilated control aortic samples (26). Moreover, an upregulated expression of MMP-12 was observed in the aortic wall of an abdominal AA model in mice (27,28). However, numerous experiments have indicated that the conclusions of animal experiments are not necessarily applicable to humans, and other issues including reverse causality and unmeasurable interference in the association study in the population (29). Moreover, it is not clear whether MMP-12 is elevated before or after the occurrence of AD. In spite of previous studies have revealed that MMP-12 was associated with AD and AA (25-29), however, observational studies cannot reliably determine causality due the potential for confounding or reverse causality. Hence, to precisely determine the causal relationship between MMP-12 and AD/AA, MR analysis was conducted to characterize the bidirectional genetic associations between these factors. In our study, serum MMP-12 levels were causally associated with an increased risk of AD and AA. It has been argued that MMPs may be increased after the occurrence of aortic diseases, but we did not find that AD/AA exerted causal effects on MMP-12 levels.

The specific regulatory mechanism of MMPs related to the pathogenesis of AD and AA remains unclear. Several studies have demonstrated the potential mechanism of MMP-12 in the development of AD and AA. In a clinical trial, MMP-12 was proven to be positively correlated with body mass index (BMI) (30), which was a risk factor for AD. Other studies have found that interleukin-3 (IL-3) can activate macrophages to secrete MMP-12 through JNK and AP-1 signaling pathways, which are involved in the emergence of TAA and dissection (TAAD). It has been speculated that the activation of the IL-3/IL-3Rβ/MMP-12 pathway plays a key role in the pathogenesis of TAAD (19). Zheng *et al.* demonstrated that p110δ deletion can cause a considerable decomposition of ECM and promote macrophages to gather to the aortic wall and contribute to the development and progression of aortic atherosclerosis by activating the protein-1/MMP-12 pathway (31).

Other research suggests that MMPs are closely related to lung diseases such as chronic obstructive pulmonary disease (COPD), asthma, and emphysema. The genetic polymorphism of MMP-12 has been associated with the severity of the disease, with the inhibition of MMP-12 decreasing the likelihood of airway inflammation (32). Similarly, it has been reported that the role of MMP-12 in COPD is closely related to emphysema and that downregulation of MMP-12 expression can alleviate this effect (33). In our study, MMP-12 was closely correlated with the risk of AD and AA, suggesting that MMPs may contribute to the pathogenesis of AD and AA and can thus be considered a novel target for the prevention and treatment of aortic diseases. Moreover, arterial stiffening was reported to be a risk factor for AD (34), while MMP-12 is closely related to arterial stiffening (35) and atherosclerosis (36). In Liu *et al.*'s animal experiment, elimination of MMPs could reduce the risk of atherosclerosis and arteriosclerosis (37). In another study, knocking out MMP-12 could significantly reduce the proliferation of aneurysms in mice (20). Finally, pharmacological inhibition of MMP-12 activity with a phosphinic peptide inhibitor was reported to retard AA formation and progression in angiotensin II-infused Apoe$^{-/-}$ mice (38). Therefore, the pharmacological inhibitors of MMP-12 are a very promising treatment for AD or AA. At present, linvemastat (FP-020), AZD-1236, MLP-1236, as well as aderamastat (FP-025) have been proved could inhibit MMP-12 and reduce the promoting effect of MMP-12 on fibrosis in chronic diseases. Therefore, targeting inhibition of MMP-12 activity or decreased MMP-12 levels may be a potential therapeutic target for AD and AA. However, considered that the relatively lower incidence of AA which compared to other chronic diseases, there were limited related clinical researches for investigating the clinical effect of pharmacological inhibitors MMP-12 on AD or AA. Therefore, further investigation should be undertaken to determine the efficacy of MMP-12 inhibition on AD and AA.

The strength of this study is that it is the bidirectional MR analysis to assess the genetic relationship between serum MMP-12 levels and AD/AA. The application of genetic variants as IVs can greatly reduce confounders and reverse causality in observational studies. In addition, the heterogeneity and sensitivity ensure the credibility of the study.

Limitations

First, $P<5\times10^{-6}$ and 5×10^{-7} were used as important indicators to screen the IVs of AD and AA, which might have rendered the SNPs less specific. Second, since our MR analysis used summary estimates instead of individual patient data, we did not perform subgroup analyses based on vessel size or explore nonlinear relationships between MMP-12 and AA or AD. Thirdly, our study only analyzed European populations. Therefore, we should interpret these results cautiously, as they may not be applicable to other racial groups. The borderline statistical significance (P values near 0.05) was observed in the causal relationship at the genetic MMP12 level with AD and AA, these may need cautious interpretation and need to be further confirmed in future researches. In this study, two sample MR studies were conducted to clarify the associations of MMP-12 with AD and AA and to determine if MMP-12 is an important molecular factor in AD and AA emergence. However, the related molecular mechanisms underlying MMP-12's role in the pathogenesis of AD and AA, along with the potential therapeutic effects of blocking MMP-12 on AD and AA, are unclear and should be explored further.

Conclusions

This study shows that high serum MMP-12 levels are causally associated with an increased risk of AD and AA emergence; meanwhile, no causal effect of AD and AA on MMP-12 levels was found.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-377/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-377/prf

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-377/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

References

1. Gouveia E Melo R, Mourão M, Caldeira D, et al. A systematic review and meta-analysis of the incidence of acute aortic dissections in population-based studies. J Vasc Surg 2022;75:709-20.
2. Pierce LC, Courtney DM. Clinical characteristics of aortic aneurysm and dissection as a cause of sudden death in outpatients. Am J Emerg Med 2008;26:1042-6.
3. Li R, Zhang C, Du X, et al. Genetic Association between the Levels of Plasma Lipids and the Risk of Aortic Aneurysm and Aortic Dissection: A Two-Sample Mendelian Randomization Study. J Clin Med 2023;12:1991.
4. Tsagakis K, Pacini D, Grabenwöger M, et al. Results of frozen elephant trunk from the international E-vita Open

registry. Ann Cardiothorac Surg 2020;9:178-88.
5. Motawea KR, Rouzan SS, Elhalag RH, et al. Efficacy of thoracic endovascular aortic repair versus medical therapy for treatment of type B aortic dissection. BMC Surg 2024;24:259.
6. Wang W, Piao H, Wang Y, et al. Long-Term Outcomes of Hybrid Technique of Complicated Type B Aortic Dissection. Ann Thorac Surg 2019;107:1319-25.
7. Reutersberg B, Salvermoser M, Trenner M, et al. Hospital Incidence and In-Hospital Mortality of Surgically and Interventionally Treated Aortic Dissections: Secondary Data Analysis of the Nationwide German Diagnosis-Related Group Statistics From 2006 to 2014. J Am Heart Assoc 2019;8:e011402.
8. Isselbacher EM, Bonaca MP, Di Eusanio M, et al. Recurrent Aortic Dissection: Observations From the International Registry of Aortic Dissection. Circulation 2016;134:1013-24.
9. O'Gara PT. Cardiology patient page. Aortic aneurysm. Circulation 2003;107:e43-5.
10. Gouveia E Melo R, Silva Duarte G, Lopes A, et al. Incidence and Prevalence of Thoracic Aortic Aneurysms: A Systematic Review and Meta-analysis of Population-Based Studies. Semin Thorac Cardiovasc Surg 2022;34:1-16.
11. Mullan CW, Mori M, Bin Mahmood SU, et al. Incidence and characteristics of hospitalization for proximal aortic surgery for acute syndromes and for aneurysms in the USA from 2005 to 2014. Eur J Cardiothorac Surg 2020;58:583-9.
12. Wei L, Bu X, Wang X, et al. Global Burden of Aortic Aneurysm and Attributable Risk Factors from 1990 to 2017. Glob Heart 2021;16:35.
13. Maiorano BA, Schinzari G, Carbone C, et al. Prognostic role of circulating cytokines and inflammation indexes for avelumab maintenance in metastatic urothelial carcinoma. Front Immunol 2024;15:1401214.
14. Nénan S, Boichot E, Lagente V, et al. Macrophage elastase (MMP-12): a pro-inflammatory mediator? Mem Inst Oswaldo Cruz 2005;100 Suppl 1:167-72.
15. Goncalves I, Bengtsson E, Colhoun HM, et al. Elevated Plasma Levels of MMP-12 Are Associated With Atherosclerotic Burden and Symptomatic Cardiovascular Disease in Subjects With Type 2 Diabetes. Arterioscler Thromb Vasc Biol 2015;35:1723-31.
16. Cárcel-Márquez J, Cullell N, Muiño E, et al. Causal Effect of MMP-1 (Matrix Metalloproteinase-1), MMP-8, and MMP-12 Levels on Ischemic Stroke: A Mendelian Randomization Study. Stroke 2021;52:e316-20.
17. Curci JA, Liao S, Huffman MD, et al. Expression and localization of macrophage elastase (matrix metalloproteinase-12) in abdominal aortic aneurysms. J Clin Invest 1998;102:1900-10.
18. Song Y, Xie Y, Liu F, et al. Expression of matrix metalloproteinase-12 in aortic dissection. BMC Cardiovasc Disord 2013;13:34.
19. Liu C, Zhang C, Jia L, et al. Interleukin-3 stimulates matrix metalloproteinase 12 production from macrophages promoting thoracic aortic aneurysm/dissection. Clin Sci (Lond) 2018;132:655-68.
20. Longo GM, Buda SJ, Fiotta N, et al. MMP-12 has a role in abdominal aortic aneurysms in mice. Surgery 2005;137:457-62.
21. Sekula P, Del Greco M F, Pattaro C, et al. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. J Am Soc Nephrol 2016;27:3253-65.
22. Bell KJL, Loy C, Cust AE, et al. Mendelian Randomization in Cardiovascular Research: Establishing Causality When There Are Unmeasured Confounders. Circ Cardiovasc Qual Outcomes 2021;14:e005623.
23. Folkersen L, Gustafsson S, Wang Q, et al. Genomic and drug target evaluation of 90 cardiovascular proteins in 30,931 individuals. Nat Metab 2020;2:1135-48.
24. Jia Y, Guo D, Zhang K, et al. Causal associations of serum matrix metalloproteinase-8 level with ischaemic stroke and ischaemic stroke subtypes: a Mendelian randomization study. Eur J Neurol 2021;28:2543-51.
25. Proietta M, Tritapepe L, Cifani N, et al. MMP-12 as a new marker of Stanford-A acute aortic dissection. Ann Med 2014;46:44-8.
26. Tao M, Yu P, Nguyen BT, et al. Locally applied leptin induces regional aortic wall degeneration preceding aneurysm formation in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol 2013;33:311-20.
27. Ji K, Zhang Y, Jiang F, et al. Exploration of the mechanisms by which 3,4-benzopyrene promotes angiotensin II-induced abdominal aortic aneurysm formation in mice. J Vasc Surg 2014;59:492-9.
28. Sharma N, Khalyfa A, Cai D, et al. Chronic intermittent hypoxia facilitates the development of angiotensin II-induced abdominal aortic aneurysm in male mice. J Appl Physiol (1985) 2024;137:527-39.
29. Cheung CL, Tan KCB, Au PCM, et al. Evaluation of GDF15 as a therapeutic target of cardiometabolic diseases in human: A Mendelian randomization study. EBioMedicine 2019;41:85-90.
30. Grzechocińska B, Dąbrowski FA, Sierdzinski J, et al. The

association between serum metalloproteinase concentration, obesity, and hormone levels in reproductive-aged women. Endokrynol Pol 2019;70:49-56.
31. Zheng L, Xing L, Zeng C, et al. Inactivation of PI3Kδ induces vascular injury and promotes aneurysm development by upregulating the AP-1/MMP-12 pathway in macrophages. Arterioscler Thromb Vasc Biol 2015;35:368-77.
32. Mukhopadhyay S, Sypek J, Tavendale R, et al. Matrix metalloproteinase-12 is a therapeutic target for asthma in children and young adults. J Allergy Clin Immunol 2010;126:70-6.e16.
33. Baggio C, Velazquez JV, Fragai M, et al. Therapeutic Targeting of MMP-12 for the Treatment of Chronic Obstructive Pulmonary Disease. J Med Chem 2020;63:12911-20.
34. Wen J, Trolle C, Viuff MH, et al. Impaired aortic distensibility and elevated central blood pressure in Turner Syndrome: a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 2018;20:80.
35. Liu SL, Bae YH, Yu C, et al. Matrix metalloproteinase-12 is an essential mediator of acute and chronic arterial stiffening. Sci Rep 2015;5:17189.
36. Mahdessian H, Perisic Matic L, Lengquist M, et al. Integrative studies implicate matrix metalloproteinase-12 as a culprit gene for large-artery atherosclerotic stroke. J Intern Med 2017;282:429-44.
37. Liu SL, Bajpai A, Hawthorne EA, et al. Cardiovascular protection in females linked to estrogen-dependent inhibition of arterial stiffening and macrophage MMP12. JCI Insight 2019;4:e122742.
38. Di Gregoli K, Atkinson G, Williams H, et al. Pharmacological Inhibition of MMP-12 Exerts Protective Effects on Angiotensin II-Induced Abdominal Aortic Aneurysms in Apolipoprotein E-Deficient Mice. Int J Mol Sci 2024;25:5809.

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