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Effect of serum uric acid on the risk of aortic aneurysm and dissection: A mendelian randomization analysis

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ABSTRACT

Aortic aneurysm and dissection (AAD) are severe vascular diseases with high mortality rates. However, the causal relationship between serum uric acid levels and the occurrence of AAD remains a subject of controversy. To address this issue, we conducted a two-sample Mendelian randomization (MR) analysis to investigate whether there is a causal association between these factors. We obtained single-nucleotide polymorphisms (SNPs) data related to serum uric acid levels from the FinnGen study and data on AAD from the UK Biobank. Various two-sample MR methods, including inverse variance weighted (IVW) analysis, MR-Egger regression analysis, weighted median analysis, and contamination mixture method, were employed to assess the causal relationship between serum uric acid and the risk of AAD. Sensitivity analysis was conducted to evaluate the stability and reliability of the results. The findings revealed a positive association between serum uric acid levels and the risk of aortic aneurysm (AA) (odds ratio [OR] = 1.200, 95 % confidence interval [CI]: 1.020–1.400, P = 0.0239). However, no significant correlation was observed between serum uric acid levels and the occurrence of aortic dissection (AD) (OR = 0.893, 95 % CI = 0.602–1.326, P = 0.576). Our study, which employed MR analysis, identified a positive association between serum uric acid levels and the risk of AA. However, we did not observe a significant correlation with AD.

1. Introduction

Aortic aneurysm and dissection (AAD) is highly lethal vascular diseases. The global mortality rate for aortic diseases, including AAD, has increased from 2.49 per 100,000 (95 % CI 1.78–3.27) in 1990 to 2.78 per 100,000 (95 % CI 2.04–3.62) in 2010 over the past 20 years [1]. In recent years, with the widespread use of various auxiliary examinations and the gradual maturation of endovascular treatment, the overall mortality rates of aortic diseases, especially in developed countries, have shown a declining trend. However, the incidence of aortic diseases remains high, with the overall incidence rate of aortic dissection in Europe estimated at around 5.7–6 per 100,000 people annually, varying based on the region and time of statistics [2]. Aortic aneurysm (AA) is the second most common disease affecting the aorta, following atherosclerosis [3]. It is characterized by localized dilation of the aorta with a diameter that is 50 % larger than the expected diameter of the same aortic segment. AA are prone to the formation of thrombus, which can potentially detach and cause blockages in various organs and tissues, leading to ischemia and necrosis [4]. Aortic dissection (AD) is characterized by the presence of an intimal flap that separates the true and false lumens of the aorta, resulting ischemia in organs or limbs supplied by the false lumen [5,6]. Despite the availability of established treatment methods, such as endovascular treatment and open surgery, the high mortality rate and the long asymptomatic period in most patients present ongoing challenges in managing aortic diseases.

Studies have shown that independent risk factors for AA and AD

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include atherosclerosis, syndromic diseases (such as Marfan syndrome), traumatic injury, and obesity, in addition to gender, age, and smoking history [7–9]. Uric acid, the end product of purine metabolism, has been the focus of numerous observational studies. A multi-center retrospective cohort study comprising around 23,475 participants from various hypertension centers in Italy revealed a linear association between serum uric acid levels and both overall mortality and cardiovascular mortality. This correlation remained significant regardless of other cardiovascular risk factors. The optimal serum uric acid thresholds for predicting overall mortality and cardiovascular mortality were identified as 4.7 mg/dL and 5.6 mg/dL, respectively [10]. Similarly, a lot of studies have explored the association between serum uric acid levels and AAD. For instance, a 3.8-year nationwide community cohort study involving 47,725 participants suggested that serum uric acid may be a risk factor for mortality associated with aortic diseases [11]. Additionally, patients with AA have been found to exhibit increased levels of uric acid in their blood vessels and serum [12]. In individuals with newly diagnosed non-diabetic hypertension and ascending AA, there appears to be a positive correlation between serum uric acid levels and aortic dilation [13]. However, certain retrospective studies have produced contradictory results, indicating no significant disparity in serum uric acid levels between patients with ascending AAD and healthy controls [14,15]. It is crucial to acknowledge that these associations may be influenced by various confounding factors that are difficult to fully address in studies, and the potential risk of reverse causality cannot be discounted.

Mendelian randomization (MR) is a valuable statistical technique that employs genetic variables as instrumental variables (IVs) to establish causal relationships between risk factor exposures and disease outcomes. In situations where implementing randomized controlled trials (RCTs) is challenging, MR can provide valuable causal evidence [16]. The complex trait of serum uric acid levels, which is influenced by genetic factors, has an estimated heritability ranging from 40 % to 60 % [17]. Consequently, serum uric acid levels or gout have been utilized as exposure factors in numerous MR (MR) studies. In this study, we performed a comprehensive MR analysis to infer the potential causal relationship between hyperuricemia and AA (Fig. 1)

2. Methods

2.1. Study design

MR is a valuable method that utilizes the random allocation of genetic variations during meiosis to infer causal relationships. It employs SNPs as IVs that must satisfy three key assumptions [18]. First, the SNPs used as IVs must demonstrate strong association with the exposure of interest, in this case, uric acid levels (*p-value* < 5e-08 & *F* > 10). Second, the independence assumption requires that the SNPs used as IVs are independent of any confounding factors that may influence both the exposure and the outcome, such as other known risk factors for AA. Lastly, the exclusion restriction assumption states that the SNPs used as IVs only affect the outcome (AA) through their influence on the exposure (serum uric acid) and not through any other pathways (Fig. 1) [19].

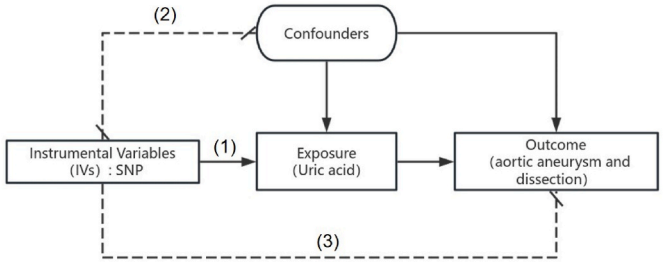

Fig. 1. Three key assumptions of MR studies are as follows: (1) SNPs are closely associated with uric acid levels; (2) SNPs are independent of other known confounding factors; (3) SNPs only affect the risk of aortic aneurysm through uric acid. Dashed lines indicate that the selected SNPs as instrumental variables are not directly associated with confounding factors and the outcome.

2.2. Data resources

The UK Biobank (UKB) provides summary data from a GWAS that investigated uric acid levels in 343,836 European participants, This data can be accessed from https://gwas.mrcieu.ac.uk/datasets (ID: ukb-d-30880_irnt). The database includes data from different genders, supporting gender-stratified analysis. The statistical data on outcomes related to AAD in the European population is available from the FinnGen genetic database, which comprises 209,366 European participants. The data can be accessed at https://r8.finngen.fi/(ID: finn-b-I9_AORTANEUR & finn-b-I9_AORTDIS) [20].

2.3. Selection of genetic instrumental variables

First, we use a threshold of *p-value* < 5e-08 and *F-value* > 10 to determine SNPs in the genome-wide association study (GWAS) of serum uric acid that are significantly and strongly associated. Then, we exclude SNPs in linkage disequilibrium (LD) using pre-specified parameters (r2 < 0.001 within a 10,000 kb range; using the European 1000 Genomes Panel) to ensure independence among the selected IVs. Finally, SNPs that do not match the result dataset and palindromic SNPs are excluded during variant harmonization, and directionally inconsistent SNPs are removed using MR Steiger [21]. We utilized PhenoScanner to identify the traits associated with each SNP, and excluded variables linked to AAD (e.g., BMI, smoking, atherosclerosis, etc.) with a significance threshold of *P-value* < 1e-05. The SNPs that passed or were excluded in the screening process are detailed in Supplementary Table 2.

2.4. Statistical analysis

The inverse-variance weighted (IVW) method, which combines the cumulative causal effects derived from the Wald ratio of each instrumental variable, has high statistical power [16]. We have accounted for potential biases from invalid instruments or pleiotropy in the estimation of IVW. Even when up to 50 % of the weights come from unreliable SNPs, the weighted median method can still produce consistent estimates. The MR-Egger method can provide reliable results even when all SNPs are invalid, but it has lower effectiveness compared to the IVW method [22,23]. Building on the three previous methods, we verified the results through a mixed contamination method. As a supplementary or alternative method, the mixed contamination method can provide more accurate causal inference results when dealing with outliers and horizontal pleiotropy [24].

2.5. Sensitivity analysis

In our analysis, we conducted a test for horizontal pleiotropy using MR-Egger. A *p-value* > 0.05 for the intercept of MR-Egger suggests no significant evidence of horizontal pleiotropy in the data, and we used Cochran's Q test to assess the heterogeneity among the estimated values of individual genetic variations. The results showed that when the *p-value* > 0.05, it indicates that there is no heterogeneity among the SNPs studied. To assess the stability of our results, we performed a leave-one-out sensitivity analysis, excluding each SNP one at a time. Funnel plots and forest plots were generated to directly investigate the presence of horizontal pleiotropy.

All *statistical* analyses were performed using R software (version 4.0.2) and TwoSampleMR (version 0.5.7). Forest plot was plotted by https://www.bioinformatics.com.cn (last accessed on 10 Oct 2023), an online platform for data analysis and visualization.

3. Results

3.1. IVs selection

We identified 50,119 SNPs (*p-value* < 5e-08) associated with serum uric acid. After adjusting for linkage disequilibrium, we found 251 independent SNPs associated with serum uric acid. Next, by matching the entire genome to the outcome, we identified 226 SNPs ($F > 10$) that were closely related to the exposure but unrelated to the outcome. After removing palindromic sequences and incompatible alleles, we obtained 216 SNPs. We did not use proxy SNPs to avoid introducing potential bias in the results. Finally, we excluded SNPs related to common risk factors for aneurysm, including smoking, atherosclerosis, hypertension, and body mass index (BMI) [6], using the PhenoScanner database. A total of 183 SNPs were selected as the final IVs for analysis. Detailed information about the genetic variants used in the MR analysis can be found in Supplementary Table 1. Moreover, data extracted from the UK Biobank database for both males and females underwent identical selection criteria and are displayed in Supplementary Tables 2 and 3 (Female: 84 SNPs; Male: 77 SNPs). The specific process of selecting SNPs is illustrated in Fig. 2.

3.2. Effects of serum uric acid on aortic aneurysm and dissection

According to our analysis and the findings presented in Table 1 and Fig. 3, there is strong evidence supporting a causal relationship between serum uric acid levels and the occurrence of AA. The instrumental variable analysis, specifically the IVW analysis, revealed a significant correlation between serum uric acid and the incidence of AA ($OR = 1.02$, 95%$CI = 1.02–1.41$, *P-value* < 0.05). There is no significant causal relationship between serum uric acid and AD ($OR = 0.893$, 95%$CI = 0.602–1.326$, *P-value* > 0.05). Considering that gender is also a risk factor for AAD (male-to-female: 3–5 to 1) [25,26], we subsequently stratified the data by gender and found that gender did not affect our research results (Table 2).

Table 1
Causal relationship, multiplicity, and heterogeneity testing between uric acid levels and aortic aneurysms and dissections.

		Serum uric acid vs AA		Serum uric acid vs AD	
Methods	IVs (SNPs)	OR(95%CI)	P-value	OR(95%CI)	P-value
IVW	183	1.204 (1.024,1.414)	0.023	0.893 (0.602,1.326)	0.576
MR-Egger	183	1.081 (0.868,1.346)	0.485	0.651 (0.381,1.113)	0.118
Weighted median	183	1.079 (0.854,1.363)	0.520	0.686 (0.395,1.189)	0.179
Pleiotropy&Heterogeneity		Intercept		Intercept	
MR-Egger intercept	183	0.004	0.158	0.014	0.090
Cochran's Q test (IVW)	183		0.359		0.131
MR-PRESSO global test	183		0.341		0.134

IVW: Inverse variance weighted analysis, MR-PRESSO: MR pleiotropy residual sum and outlier, OR: odds ratio, AA: aortic aneurysm, AD: aortic dissection.

Although both the MR-Egger and weighted median methods demonstrate consistency with the IVW method in terms of OR, the p-value indicates that the results are not statistically significant (*p-value* > 0.05). However, it is important to note that these non-significant results obtained from the MR-Egger and weighted median methods do not necessarily imply the absence of a causal relationship between the exposure and the outcome. It is crucial to consider the limitations of these methods. When outliers and confounders have been properly addressed and there is no evidence of pleiotropy or heterogeneity, we tend to place greater trust in the results obtained through the IVW

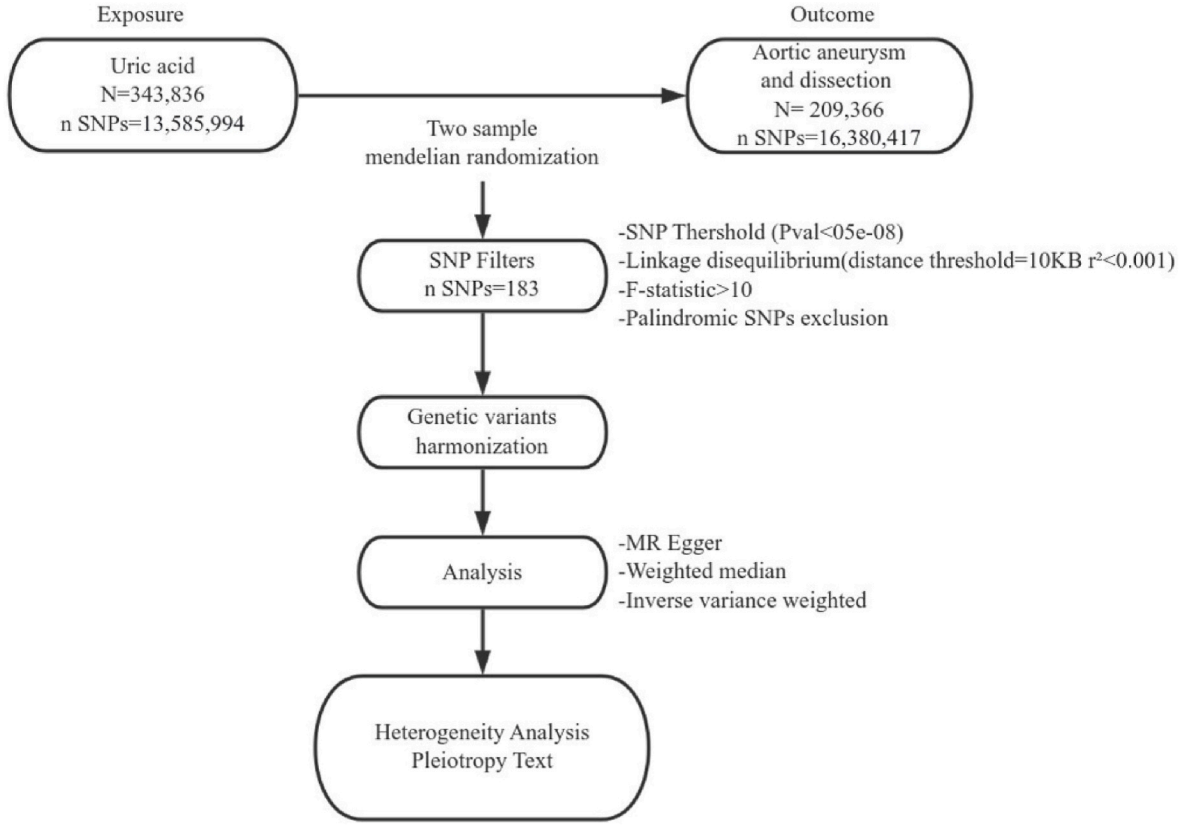

Fig. 2. The steps of Mendelian randomization (MR) analysis.

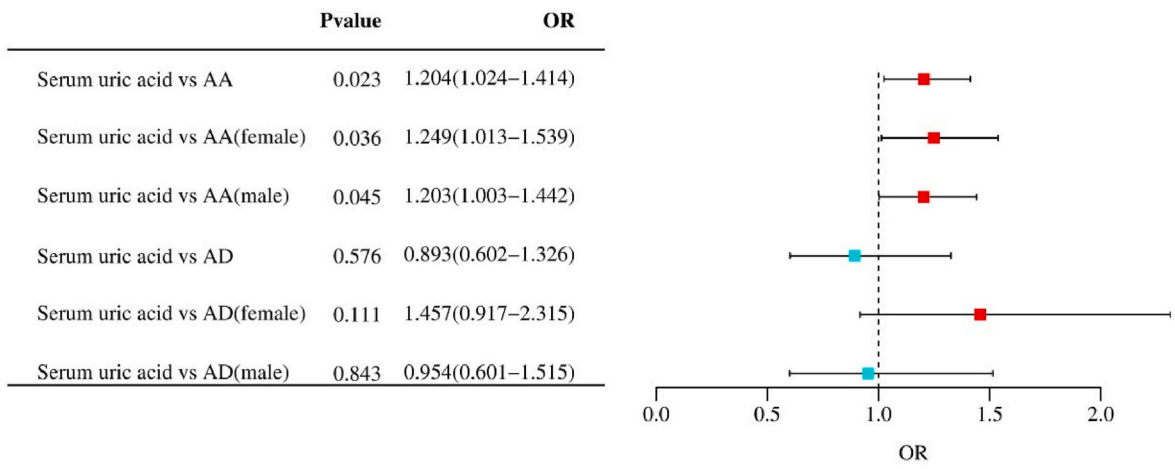

Fig. 3. Causal Relationship between Uric Acid Levels and Aortic Aneurysms and Dissections (IVW). OR: odds ratio, AA: aortic aneurysm, AD: aortic dissection.

Table 2
Causal estimates of genetically predicted serum uric acid on the risk of AAD, stratified by gender.

Female		Serum uric acid vs AA		Serum uric acid vs AD	
Methods	IVs (SNPs)	OR(95%CI)	P-value	OR(95%CI)	P-value
IVW	84	1.249 (1.013,1.539)	0.036	1.457 (0.917,2.315)	0.111
MR-Egger	84	1.143 (0.747,1.749)	0.536	0.626 (0.245,1.604)	0.332
Weighted median	84	1.304 (0.944,1.802)	0.106	1.371 (0.595,3.161)	0.457
Pleiotropy&Heterogeneity		Intercept		Intercept	
MR-Egger intercept	84	0.003	0.641	0.035	0.046
Cochran's Q test (IVW)	84		0.201		0.574
MR-PRESSO global test	84		0.223		0.129
Male		Serum uric acid vs AA		Serum uric acid vs AD	
Methods	IVs (SNPs)	OR(95%CI)	P-value	OR(95%CI)	P-value
IVW	77	1.203 (1.003,1.442)	0.045	0.954 (0.601,1.515)	0.843
MR-Egger	77	1.125 (0.784,1.615)	0.521	0.642 (0.256,1.612)	0.349
Weighted median	77	1.148 (0.853,1.544)	0.360	0.802 (0.404,1.592)	0.529
Pleiotropy&Heterogeneity		Intercept		Intercept	
MR-Egger intercept	77	0.003	0.678	0.018	0.332
Cochran's Q test (IVW)	77		0.684		0.141
MR-PRESSO global test	77		0.698		0.129

IVW: Inverse variance weighted analysis, MR-PRESSO: MR pleiotropy residual sum and outlier, OR: odds ratio, AA: aortic aneurysm, AD: aortic dissection.

method [23]. Nevertheless, to enhance the stability of our results, we further validated our findings using a mixed contamination method, as shown in Supplementary Table 5. Elevated serum uric acid levels did indeed increase the risk of aortic aneurysm (OR = 0.2, 95%CI = 0.02–0.41, P-$value$ = 0.038), but no clear causal relationship was observed with aortic dissection (OR = −0.15, 95%CI = −0.57–0.25, P-$value$ = 0.435).

The MR-Egger regression and Cochran's Q test did not provide evidence of pleiotropy or heterogeneity (Table 1). Furthermore, the MR-PROSS analysis did not detect any outliers in the dataset, and even after excluding individual SNPs, it still supports the existence of a causal relationship. Funnel plots, Scatter plot and forest plots can be found in Supplementary Figs. 1–3.

4. Discussion

In this study we attempt to use a two-sample MR analysis, which will prove that elevated serum uric acid, as caused by genetic factors, is related to susceptibility to AAD among the European population. The results suggest that high serum uric acid level may predispose to increase in AA risk although no direct correlation was found with AD, and this result lays important groundwork for future research towards elucidation of molecular mechanism and etiology link between elevated serum uric acid and AA development. It also reinforces MR analysis is a widespread and important practice in medicine.

Previous studies have suggested a potential association between serum uric acid levels and AA, although it is not considered an independent risk factor. Patetsios, Rodino [12]were the first to discover elevated levels of uric acid in the vascular walls of AA and proposed that increased activity of aortic intimal xanthine oxidase may lead to uric acid deposition and trigger aortic damage, ultimately resulting in the formation of an AA. Wang, Tsai [27]conducted a study involving 121, 236 patients with gout and 121,236 individuals in the control group. The study showed an increase of AA among patients with gout (HR = 2.465, P-$value$ < 0.001). Additionally, treated patients were at lower risk of hypertension than untreated (HR = 0.489, P-$value$ < 0.001). This supports an argument that there exists a causality between uric acid and AA.

A recent line of studies has explored how uric acid may relate to AAD. The study was conducted by Yang, Wu [28] in a mouse model of thoracic aortic aneurysm and dissection (TAAD). TAAD in mice was inhibited by the addition of the uric acid-lowering drug allopurinol to drinking water. They suggested that hyperuricemia promotes an inflammatory response and TAAD development via FcgR-triggered ERK1/2 phosphorylation in macrophages. However, our research could not demonstrate the causal association between serum uric acid and AD unlike causal relationships between serum uric acid and AA. While Zhang, Xu [29]suggested that there could be a connection between in-hospital mortality and serum uric acid levels in patients with acute type A aortic dissection, but this disease is not common, especially in developed countries where the complexity It is difficult to observe the relationship directly since traditional observational studies are highly vulnerable to interference by other undisclosed or unadjusted confounders (biases), which could affect study outcomes or results. Previous research has primarily focused on using uric acid as a predictive factor for in-hospital mortality in aortic dissection patients, rather than

considering it as a causative factor [30,31]. While some retrospective studies have shown higher uric acid levels in aortic dissection patients compared to a normal control group [32], the association between uric acid and various metabolic diseases complicates defining it as an independent risk factor for aortic dissection. Thus, MR as an analytical method with widely used in genetic research to infer causal relationships between exposure factors and outcomes by SNPs. It leverages principles of genetics to simulate a situation similar to random allocation of treatment and control groups within the study population, while also controlling for potential confounding variables that may influence the outcomes to approach provides more reliable and accurate results.

The causal relationship between uric acid and AA, as concluded in the study, suggests that uric acid may play a role in the development or progression of AA. In addition to the high uric acid mentioned in Yang, Wu [28] triggering macrophage ERK1/2 phosphorylation to promote inflammation and the development of AA through FcgR, Wang, Tsai [33]analyzed data from 107 AA patients and found that patients with serum uric acid levels higher than 9 mg/dl had a higher AA growth rate compared to those with serum uric acid levels between 4 and 7.9 mg/dl. The study revealed that uric acid mediates AA development through activation of URAT1/ERK1/2/ROS/MMP-9. Similarly, the study in Rodríguez-Rovira, Arce [34], the use of allopurinol (a drug that reduces uric acid levels in the body and prevents crystal formation) reduced related large vessel H2O2 generation and decreased the overexpression of NOX4 and MMP2 transcription in a Marfan syndrome mouse model. Overall, uric acid could be playing a role in creating AA by taking part in oxidative stress, inflammation, and endothelial dysfunction. However, for AD, the study did not find a causal relationship with uric acid. The reasons behind these differential findings could be multifactorial and may require further investigation. Uric acid is considered an independent risk factor for conditions such as atherosclerosis, type 2 Diabetes and hypertension [35,36], which may in turn indirectly contribute to the onset of AD. Yet, findings from MR analysis using large-scale GWAS databases suggest that a direct causal link between uric acid levels and AD is not evident. A recent epidemiological study on aortic aneurysm and aortic dissection mentioned that these diseases are common in aortic conditions [6], sharing some common risk factors, such as systemic hypertension, weight training leading to increased aortic wall stress, and atherosclerosis. However, they also have distinct risk factors; aortic dissection is more associated with trauma and substance abuse (especially cocaine), while aortic aneurysm is more linked to aging and degenerative changes like atherosclerosis. Furthermore, their sites of occurrence differ; aortic dissection and rupture mainly occur in the ascending aorta and aortic arch, while aortic aneurysms more frequently arise in the abdominal aorta, especially below the renal arteries. Interestingly, a recent study on the mechanisms of aortic aneurysm and dissection pointed out some differences in the pathogenesis of aortic aneurysm and aortic dissection [37], the critical lesion in aortic dissection is the rupture of the intima, whereas in aortic aneurysm, the key pathology is the expansion and degeneration of the entire vessel wall. In aortic dissection, high homocysteine levels exacerbate vascular wall damage by affecting endothelial and smooth muscle cell function, representing a crucial pathological factor. Conversely, in aortic aneurysm, metabolic disorders lead to complex cellular function changes, resulting in endothelial dysfunction, smooth muscle cell phenotypic transformation, and extracellular matrix degradation, among other pathological processes. These studies may explain why there is no clear causal relationship between serum uric acid and aortic dissection. Of course, further comprehensive research is necessary to fully understand the specific mechanisms and correlations between uric acid and AD.

In this study, the MR analysis also has limitations: although MR analysis has been established that they are cause-and-effect variables, but methodological experts warn about the application of these results in estimating therapeutical intervention's influence on risk factors within clinical settings [38]. It is also notable that there are limits on the causality between the two factors. Thoracic aortic aneurysms and abdominal aortic aneurysm involve differing risk factors and pathophysiological mechanism [6]. Hence, the causality between serum uric acid might be different in these dissimilar subtypes of aneurysms. Finally, the GWAS database we utilized originated from European populations, potentially introducing bias when extrapolating the research findings to diverse populations. Similarly, our exposure samples are obtained from the UK, whereas the outcome samples originate from Finland. Varying populations or geographic regions may exhibit unique genetic backgrounds, potentially introducing genetic structure bias. We anticipate acquiring data from a variety of ethnic sources in the future to facilitate the establishment of universally applicable conclusions in subsequent research.

5. Conclusion

Overall, we have conducted a two-sample MR analysis that has offered genetic proof of the causality connection between serum uric acid and AAD. Increased levels of uric acid may be risky for aortic aneurysms but without significant co-relation with aortic dissection. This study highlights the need for further investigations into the potential association between serum uric acid and AA, as well as its possible role in the prevention and treatment of the disease.

Availability of data and materials

The UK Biobank (UKB) provides summary data from a GWAS that investigated uric acid levels in 343,836 European participants. This data can be accessed from https://gwas.mrcieu.ac.uk/datasets (ID: ukb-d-30880_irnt).

The statistical data on outcomes related to AAD in the European population is available from the FinnGen genetic database, which comprises 209,366 European participants. The data can be accessed at https://r8.finngen.fi/(ID: finn-b-I9_AORTANEUR & finn-b-I9_AORTDIS).

Ethical approval

We used publicly available summary-level data. Ethical approval and informed consent for each included study can be determined in each original publication. Therefore, no additional ethical approval was needed.

Human and animal rights and informed consent

All participants of the original studies included in the GWASs provided informed consent.

Consent for publication

Not applicable.

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CRediT authorship contribution statement

Zi-Peng Lin: Writing – original draft, Data curation, Conceptualization. **Hu-Qiang He:** Investigation, Funding acquisition, Formal analysis. **Yierpani Aierken:** Resources, Project administration, Methodology. **Ya Wu:** Writing – review & editing, Writing – original

draft, Visualization, Validation. **Yong Liu:** Writing – review & editing, Project administration, Investigation.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

I have shared the link to my date at the Attach file

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2024.101743.

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