Heliyon 10 (2024) e31535

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Association of serum uric acid level with intracranial aneurysms: A Mendelian randomization study

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ARTICLE INFO

Keywords:
Uric acid
Intracranial aneurysm
Subarachnoid hemorrhage
Mendelian randomization

ABSTRACT

Objective: Numerous studies have posited the involvement of serum uric acid (SUA) in the pathogenesis and progression of various cardiovascular diseases, particularly aortic aneurysms. However, the casual effect of SUA level on intracranial aneurysms (IAs) was rarely studied. Consequently, we aimed to explore the causal association between SUA and IAs using Mendelian randomization (MR) analysis.

Methods: We conducted a two-sample MR analysis with SUA as the exposure variable and IAs as the outcome variable. Genome-wide association study (GWAS) datasets for SUA were acquired from the Open GWAS catalog, including 389,404 European and 129,405 East Asian individuals. The dataset for IAs was sourced from a meta-analysis of GWASs comprising 317,636 individuals across different ancestral populations (European: 7495 cases and 71,934 controls; East Asian: 3259 cases and 234,948 controls). The MR analyses were performed according to populations (European and East Asian) and IAs status [unruptured IAs (uIAs) or aneurysmal subarachnoid hemorrhage (aSAH)], respectively. The inverse variance weighted (IVW) method was employed as primary analysis to discern causal estimates.

Results: Our findings revealed that an elevated genetically predicted SUA level (mg/dL) correlated with an increased risk of IAs among the European population (OR = 1.29 [95%CI:1.05–1.57], P = 0.013) and East Asian population (OR = 1.56 [95%CI: 1.27–1.92], P < 0.001). Among European individuals, subgroup analysis indicated a persistent causal association of SUA with uIAs (OR = 1.50 [95%CI: 1.08–2.08], P = 0.015) and aSAH (OR = 1.26 [95%CI: 1.00–1.60], P = 0.049). However, subgroup analysis in East Asian populations was not conducted due to the lack of separate data on uIAs and aSAH.

Conclusions: Our MR analysis demonstrated a causal relationship between elevated SUA levels and an amplified risk of IAs. Further rigorous investigations are imperative to provide evidence and elucidate the underlying mechanisms.

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https://doi.org/10.1016/j.heliyon.2024.e31535
Received 8 January 2024; Received in revised form 17 May 2024; Accepted 17 May 2024
Available online 18 May 2024

1. Introduction

Intracranial aneurysms (IAs) represent localized pathological dilatations on the cerebral artery characterized by abnormally weak vessel walls [1]. Among patients devoid of comorbidities, the prevalence of unruptured IAs (uIAs) stands at approximately 3.2 %, generally occurring at a mean age of 50 years [2]. Typically, individuals with uIAs are asymptomatic, and these conditions may remain undetected until rupture occurs. However, once ruptured, they lead to aneurysmal subarachnoid hemorrhage (aSAH) often resulting in severe outcomes. Despite contemporary neurosurgical intensive care, the mortality rate of aSAH remains around 30–40 % [3], and nearly half of survivors experience disabilities or long-term cognitive impairment [4].

Serum uric acid (SUA) constitutes a metabolite resulting from the breakdown of DNA and RNA within the purine metabolic pathway. Multiple studies have postulated the involvement of SUA in the onset and progression of atherosclerosis and other cardiovascular diseases [5–8]. For example, the increase of SUA levels may also exacerbate the development of aortic aneurysms [9,10]. Given their similar histopathological characteristics, the impact of SUA levels on IAs initiation was uncertain. Furthermore, the meta-analysis has demonstrated that elevated SUA levels pose a risk factor for hemorrhagic stroke in females [11], and its increase also potentially contribute as a risk factor for intracerebral hemorrhage among the elderly [12]. Nevertheless, the causal relationship between SUA levels and IAs progression (aSAH) remains unknown. Therefore, it is of great importance to reveal the potential effect of SUA levels on IAs initiation and its progression, which contributes to reduce the IAs risk through monitoring and regulating SUA level.

Mendelian randomization (MR) employs genetic variants to ascertain whether an observed association between a risk factor and an outcome aligns with a causal effect [13]. Relying on the random distribution of single-nucleotide polymorphisms (SNPs) during meiosis, MR analysis offers a potential means to mitigate residual confounding inherent in conventional observational studies [13]. In this study, our objective was to investigate the potential association between SUA levels and the incidence of IAs (including uIAs and aSAH) using MR, thereby offering new insights for clinical intervention.

2. Materials and methods

2.1. Study design and ethical approval

Two-sample MR was designed based on three fundamental assumptions (Fig. 1), utilizing SUA as the exposure variable and IAs (including uIAs and aSAH) as the outcome variable. All genome-wide association study (GWAS) summary statistics used in the analysis were publicly accessible, and no local patients were involved. Thus, approval from an ethics committee was deemed unnecessary.

2.2. Data sources for SUA and IAs

The data sources and detailed information regarding the GWASs for SUA and IAs are listed in Table 1 [14–16]. As the exposure variable, summary statistics data for SUA were gathered from the Open GWAS catalog (https://www.ebi.ac.uk/gwas/home), incorporating a dataset comprising 389,404 individuals of European ancestry [14], and another dataset including 129,405 East Asian individuals [15]. As for the outcome variable, we utilized a meta-analysis of GWASs data for IAs, which included 317,636 individuals of cross-ancestry origin (European: 7495 cases and 71,934 controls; East Asian: 3259 cases and 234,948 controls) [16].

2.3. Selection of instrumental variables (IVs) for SUA

The procedural steps for our MR study analysis are depicted in Fig. 2. To ensure a robust association, the IVs (SNPs) were required to exhibit a significant statistical difference with SUA at the genome-wide level (P-value$<5 \times 10^{-8}$). Moreover, the independence of selected SNPs was verified by clumping variants in linkage disequilibrium ($r^2 < 0.001$; clumping window, 10,000 kb), while

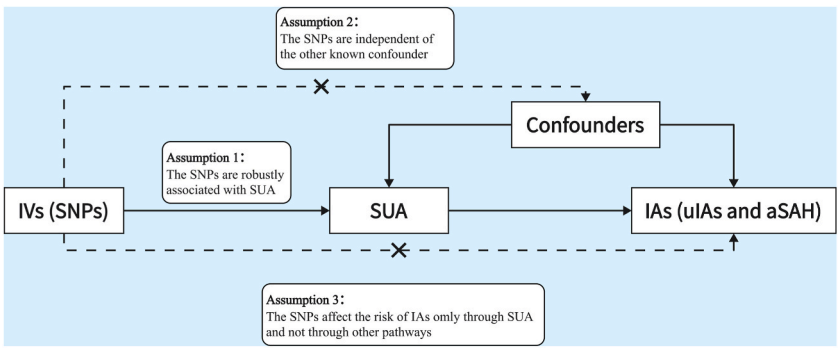

Fig. 1. Three fundamental assumptions of the Mendelian randomization (MR) analysis. IVs, instrumental variables; SNP, single-nucleotide polymorphisms; SUA, serum uric acid; IAs, intracranial aneurysms; uIAs, unruptured intracranial aneurysms; aSAH, aneurysmal subarachnoid hemorrhage.

palindromic SNPs were excluded. Subsequently, genetic variants harmonization was conducted, followed by the calculation of F-statistics for each IV. Any IV with an F-statistic lower than 10 was excluded [17]. Further refinement involved utilizing the PhenoScanner database (https://www.phenoscanner.medschl.cam.ac.uk) to eliminate IVs significantly correlated with known confounders such as systolic blood pressure, diastolic blood pressure, smoking history, and insomnia [18].

2.4. Statistical analysis

The primary method employed for analysis was the inverse variance weighted (IVW) method under random effects [19]. Additionally, MR-Egger [20] and weighted median [21] analyses were performed. Meaningful MR results were considered to have been achieved when the IVW method yielded a significant difference (p-value$<$0.05) and the direction of β values aligned with those of the other two methods. Odds ratios (OR) for the outcomes per unit increase in exposure, along with their corresponding 95 % confidence intervals (CI), were reported as estimates of MR results. These were visualized using forest plots and scatter plots. The MR analyses were performed among different subgroups by stratifying patients with populations (European and East Asian) and IAs status (uIAs or IAs). It should be noted that subgroup analysis regarding the IAs status in East Asian populations was not conducted due to the lack of separate data on uIAs and aSAH. For sensitivity analysis, MR-Egger intercept analysis, Cochrane's Q test, leave-one-out analysis, and funnel plots were applied. The presence of pleiotropy was assessed using the MR-Egger intercept analysis, where a p-value $<$0.05 indicated its existence. Heterogeneity among selected SNPs was evaluated through Cochrane's Q test, with a p-value $<$0.05 indicating its presence. The leave-one-out analysis was employed to detect whether the results of IVW would be influenced by excluding any single SNP. Furthermore, the symmetry of funnel plots was used for visual assessment of heterogeneity.

All analyses were conducted using the TwoSampleMR package in R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Overview

In this study, four distinct MR analyses were conducted, delineated by population (European or East Asian) and status of IAs (uIAs or IAs). The IVs employed for these MR analyses are documented in the supplementary materials (Tables S1, S2, S3, S4). The main findings from MR analyses are presented in Table 2, while the estimates derived from the IVW methods are visually depicted in Fig. 3. Additionally, we have included forest plots, scatter plots, leave-one-out plots, and funnel plots for each MR analysis in the supplementary material.

3.2. Causality between SUA and risk of IAs for European population

A set of 155 SNPs served as IVs (Table S1, Supplementary Fig. S1a). The IVW analysis employing random effects illustrated that genetically predicted 1 mg/dL increase in SUA level had a significant causal effect on the increased risk of IAs among European population (Table 2, OR = 1.29 [95%CI: 1.05–1.57], P = 0.013). MR methods containing MR-Egger, Weighted median methods, and IVW showed same direction (Supplementary Fig. S1b), which suggested the significant causal effect of genetically predicted SUA levels on the IAs. The MR-Egger intercept analysis indicated no presence of horizontal pleiotropy (P = 0.398). Although funnel plots (Supplementary Fig. S1c) did not show obvious heterogeneity, Cochrane's Q test detected a significant heterogeneity (Cochrane's Q = 193.87, P = 0.014), thus necessitating the use of a random effect within the IVW method. Leave-one-out sensitivity analysis plots

Table 1
Details of datasets analyzed in this study.

Exposure/ outcomes	Author (years)	Population (cases)	Data source (subset of outcomes)	Case (n)	Control (n)	SNP size
SUA	Mbatchou J (2021) [14]	European	https://www.ebi.ac.uk/gwas/studies/GCST90014015	389,404	NA	10,783,684
	Sakaue S (2021) [15]	East Asian	https://www.ebi.ac.uk/gwas/studies/GCST90018757	129,405	NA	12,499,459
IAs	Bakker MK (2021) [16]	Cross-ancestry	https://doi.org/10.6084/m9.figshare.11303372	10,754	306,882	3,527,309
		European (uIAs and aSAH)	(IA.GWAS.BakkerMK.2020.sumstats.Stage_1.txt.gz)	7495	71,934	4,484,251
		European (uIAs)	(IA.GWAS.BakkerMK.2020.sumstats.uIA-only.txt.gz)	2070	71,934	4,445,233
		European (aSAH)	(IA.GWAS.BakkerMK.2020.sumstats.SAH-only.txt.gz)	5140	71,934	4,480,722
		East Asian (uIAs and aSAH)	(IA.GWAS.BakkerMK.2020.sumstats.EastAsianSubset.txt.gz)	3259	234,948	5,897,108

SNP, single nucleotide polymorphism; SUA, serum uric acid; IAs, intracranial aneurysms; uIAs, unruptured intracranial aneurysms; aSAH, aneurysmal subarachnoid hemorrhage.

demonstrated that no single SNP was likely to have influenced the causal association (Supplementary Fig. S1d).

3.3. Causality between SUA and risk of uIAs for European population

Using 152 selected SNPs as IVs (Table S2, Supplementary Fig. S2a), the IVW analysis suggested that increased genetically predicted SUA levels (mg/dL) corresponded to a heightened risk of uIAs among European individuals (Table 2, OR = 1.50 [95 % CI: 1.08–2.08], P = 0.015). The risk of IAs would increase by 50 % with per mg/dL increase of SUA. This relationship remained consistent with MR-Egger method (OR = 2.34 [95%CI: 1.27–4.31], P = 0.007), and scatter plot indicated their significant association (Supplementary

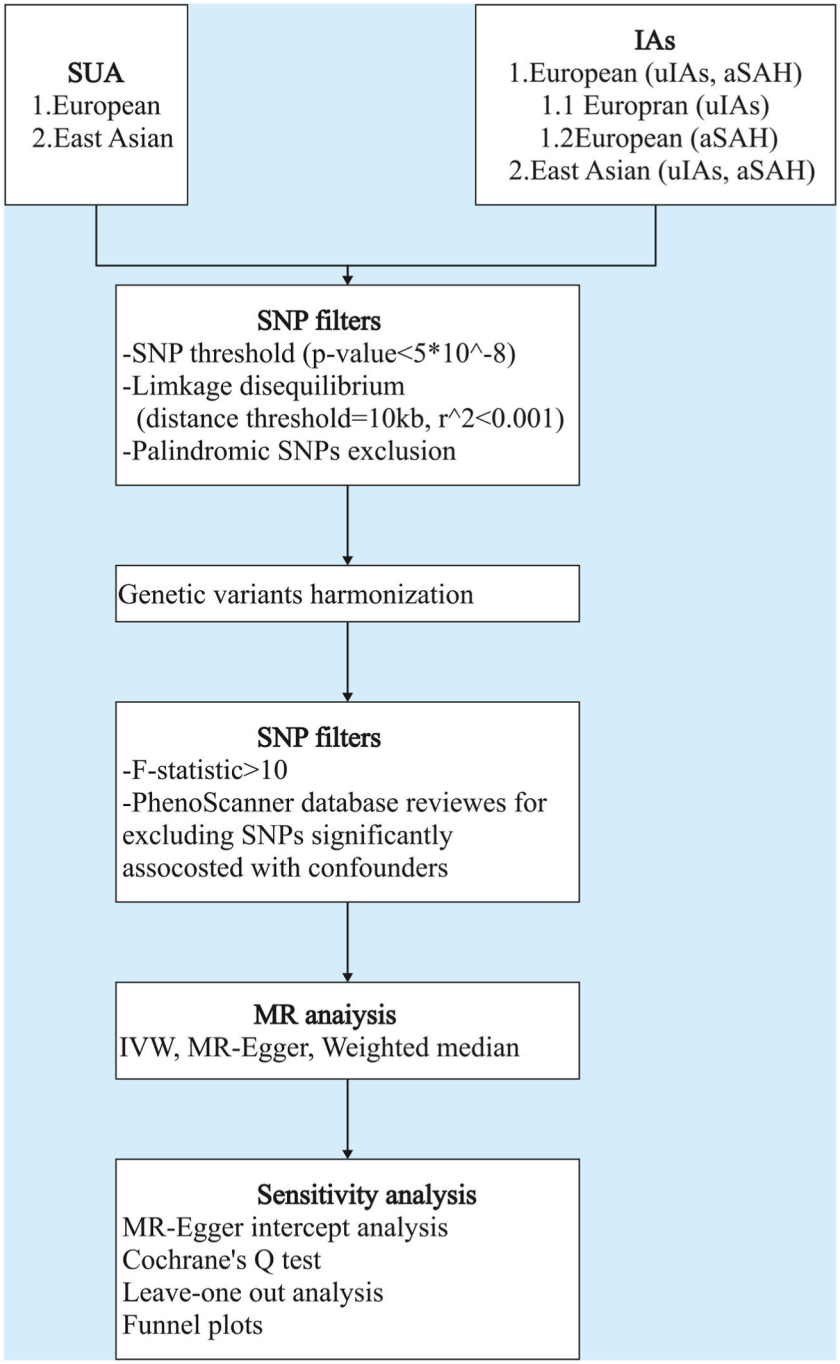

Fig. 2. The steps of Mendelian randomization (MR) analysis. SUA, serum uric acid; IAs, intracranial aneurysms; uIAs, unruptured intracranial aneurysms; aSAH, aneurysmal subarachnoid hemorrhage; SNP, single-nucleotide polymorphisms; IVW, inverse variance weighted.

Table 2
Causal associations between genetically predicted serum uric acid levels and intracranial aneurysms.

Population (cases)	Method	Number of SNPs	OR	95%CI	P
European (uIAs and aSAH)	IVW-random effects	155	1.29	1.05–1.57	0.013
	Weighted median	155	1.35	0.96–1.89	0.083
	MR-Egger	155	1.46	1.02–2.09	0.038
	Cochrane's Q (IVW) = 193.87 (P = 0.014); MR-Egger intercept = −0.0035 (P = 0.398)				
European (uIAs)	IVW-random effects	152	1.50	1.08–2.08	0.015
	Weighted median	152	1.30	0.74–2.29	0.369
	MR-Egger	152	2.34	1.27–4.31	0.007
	Cochrane's Q (IVW) = 129.48 (P = 0.897); MR-Egger intercept = −0.0113 (P = 0.094)				
European (aSAH)	IVW-random effects	155	1.26	1.00–1.60	0.049
	Weighted median	155	1.46	1.01–2.12	0.044
	MR-Egger	155	1.38	0.91–2.10	0.128
	Cochrane's Q (IVW) = 196.11 (P = 0.012); MR-Egger intercept = −0.0025 (P = 0.604)				
East Asian (uIAs and aSAH)	IVW-random effects	42	1.56	1.27–1.92	$3.0*10^{-5}$
	Weighted median	42	1.60	1.19–2.15	0.002
	MR-Egger	42	1.51	1.08–2.21	0.042
	Cochrane's Q (IVW) = 45.46 (P = 0.292); MR-Egger intercept = 0.0020 (P = 0.829)				

SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; IAs, intracranial aneurysms; uIAs, unruptured intracranial aneurysms; aSAH, aneurysmal subarachnoid hemorrhage; IVW, inverse variance weighted.

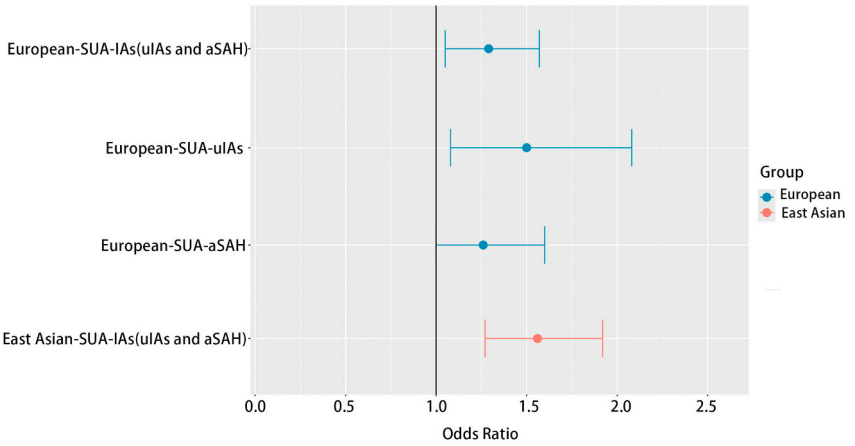

Fig. 3. Causal associations between genetically predicted serum uric acid levels and intracranial aneurysms. OR, odds ratio; CI, confidence interval; SUA, serum uric acid; IAs, intracranial aneurysms; uIAs, unruptured intracranial aneurysms; aSAH, aneurysmal subarachnoid hemorrhage.

Fig. S2b). Notably, there were no indications of horizontal pleiotropy (P = 0.094) or observed heterogeneity (Cochrane's Q = 129.48, P = 0.897; Supplementary Fig. S2c). No single SNP influenced their causal association (Supplementary Fig. S2d).

3.4. Causality between SUA and risk of aSAH for European population

With 155 SNPs serving as IVs (Table S3, Supplementary Fig. S3a), the IVW analysis incorporating random effects demonstrated that heightened genetically predicted SUA levels (mg/dL) were linked to an increased risk of aSAH among European individuals (Table 2, OR = 1.26 [95%CI: 1.00–1.60], P = 0.049), and scatter plot containing 3 MR test methods indicted the significant causal association between them (Supplementary Fig. S3b). Horizontal pleiotropy was absent (P = 0.094), but significant heterogeneity was detected (Cochrane's Q = 196.11, P = 0.012; Supplementary Fig. S3c). No single SNP influenced this causal association (Supplementary Fig. S3d).

3.5. Causality between SUA and risk of IAs for East Asian population

Utilizing 42 SNPs as IVs (Table S4, Supplementary Fig. S4a), the IVW method revealed that raised genetically predicted SUA levels (mg/dL) were associated with an increased risk of IAs among the East Asian population (Table 2, OR = 1.56 [95%CI: 1.27–1.92], P < 0.001). This connection proved consistent across MR-Egger (OR = 1.51 [95%CI: 1.08–2.21], P = 0.042) and weighted median (OR = 1.60 [95%CI: 1.19–2.15], P = 0.002) methods. Three MR test methods showed consistent direction and no single SNP influenced their significant association (Supplementary Figs. S4b and S4d). No evidence of horizontal pleiotropy (P = 0.829) or heterogeneity

(Cochrane's Q = 45.46, P = 0.292; Supplementary Fig. S4c) was observed.

4. Discussion

In this MR study, we investigated the causal relationship between SUA levels and the incidence of IAs. Our findings indicate that elevated SUA levels were associated with an increased risk of IAs among both European and East Asian populations. Given the availability of datasets for uIAs and aSAH in the European population, we conducted subgroup analyses, revealing that heightened SUA levels may also elevate the likelihood of uIAs and aSAH. These findings might provide potential implications for understanding the pathophysiology of IAs and offer new insights for clinical intervention.

The scarcity of prior research on the relationship between SUA and IAs posed challenges in comparing our findings with existing literature. Moreover, the mechanisms underlying the causality between elevated SUA and the heightened risk of IAs remain unclear. Nevertheless, studies on SUA in various cardiovascular diseases [22] and aortic aneurysms [9,10] suggest that SUA may induce inflammation, oxidative stress, and endothelial dysfunction in vessel walls [22]. Coincidentally, these pathophysiological mechanisms could be implicated in the development, progression, and rupture of IAs [23–25].

Inflammation plays a pivotal role across different stages of IAs from formation to rupture [23], and it appears that SUA may contribute to aortic aneurysm formation via inflammatory pathways. Studies by Yang L et al. revealed that hyperuricemia could induce the formation of thoracic aortic aneurysms and the dissection by activating Fc gamma receptors (FcγR)-mediated extracellular regulated kinase 1/2 (ERK1/2) phosphorylation and macrophage inflammation, which could be reversed by urate-lowering therapy in mice model [9]. Meanwhile, Wang JC et al. also indicated that hyperuricemia might exacerbate the development of abdominal aortic aneurysms via the urate transporter 1 (URAT1)/ERK/matrix metalloproteinase (MMP)-9 signaling pathway [10]. These two studies indicated the proinflammatory effects of SUA on the formation of aortic aneurysms. Thus, further investigation regarding its role in IAs is warranted.

Oxidative stress is known to contribute to the development and rupture of IAs, potentially exacerbated by enhanced inflammation [24]. Uric acid exhibits potent antioxidant properties at normal levels; however, heightened SUA levels can diminish this capability, thereby increasing oxidative stress [26]. Oxidative stress is caused by the increased production and/or decreased removal of free radicals, which might induce DNA damage, cellular toxicity, and apoptosis [27], contributing to endothelial injury, smooth muscle cell phenotype switching, matrix remodeling, and programmed cell death within the IAs wall during its lifecycle [24,28].

Through the increased oxidative stress and inflammation, the uric acid absorbed into endothelial cell (EC) could cause endothelial dysfunction, thereby contributing to the genesis of IAs [29]. This process may cause interendothelial gap formation, augmented paracellular permeability, and subsequent recruitment and infiltration of inflammatory cells [25]. Thus, there exists a close interplay between inflammation, oxidative stress, and endothelial dysfunction induced by elevated SUA [22], which plays a fundamental role in the pathogenesis of IAs [23–25].

Given the observed causal relationship between heightened SUA levels and increased IAs risk, individuals with hyperuricemia may be considered at elevated risk for IAs. Measures to reduce SUA levels, such as dietary modification or pharmacological agents, might be explored as preventive strategies. However, J-shaped associations between SUA levels and cardiovascular event risks, indicating elevated risk at low SUA levels, have been reported in epidemiological studies [30,31]. This suggests that maintaining SUA within a normal range may be crucial, considering its antioxidant capabilities. Nonetheless, further high-quality studies are necessary to confirm the causality between SUA and IAs and to explore the impact of urate-lowering therapy on IAs.

Finally, the presence of heterogeneity needs to be taken into consideration. The IVs from different analysis platforms, experiments, populations, etc. may have heterogeneity and ultimately affect the results. In this study, we conducted random effect IVW and median analyses, which has a certain tolerance for heterogeneity. Moreover, considering the differences in the samples themselves, we stratified the samples according to certain characteristics and conducted randomization analysis in each subgroup to reduce the impact of heterogeneity.

4.1. Limitations

Our study had several limitations. Firstly, we minimized population stratification bias by performing all MR analyses using European and East Asian individuals. However, our findings may not be generalizable to other populations. Secondly, subgroup analysis on uIAs and aSAH was not conducted for East Asian populations, as no separate data on uIAs and aSAH was available. However, our results showed that no evident heterogeneity was observed in East Asian populations although we failed to perform the subgroup analysis, suggesting the stability of our results. Additionally, the causal association between SUA and aSAH in the European population yielded a positive result close to the threshold, and significant heterogeneity was detected in two results of Cochrane's Q test, potentially impacting the robustness of our findings. Finally, we did not consider the use of uric acid-lowering medications in this MR analysis due to constraints in exposure data.

5. Conclusions

In conclusion, our MR study suggested a causal relationship between elevated SUA levels and an increased risk of IAs in both European and East Asian populations. Subgroup analysis among European individuals further indicated a causal association of elevated SUA with both uIAs and aSAH. This novel insight sheds light on the potential role of SUA in the pathophysiology of IAs and emphasized the need for further research to elucidate underlying mechanisms. Our findings have the potential to guide preventive and

therapeutic strategies, offering new avenues to reduce the burden of IAs. Further research, both in experimental models and diverse clinical populations, is required to validate and expand upon our findings.

Data availability statement

Data will be made available on request.

Funding

This work was supported by the following grants: the Project of NINGBO Leading Medical & Health Discipline [No. 2022-F04], the Project of Science and technology on Medicine and Health in Zhejiang Province [No. 2024KY291], and the Ningbo Natural Science Foundation [No. 2021J284], and the Doctoral Development Foundation of Lihuili Hospital [No. 2022BSKY-YGF].

CRediT authorship contribution statement

Gengfan Ye: Writing – original draft, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Wei Chen:** Writing – original draft, Validation, Formal analysis, Conceptualization. **Hongcai Wang:** Writing – review & editing, Validation, Methodology. **Xuebin Wen:** Validation, Methodology, Formal analysis, Data curation. **Zhenqiang Li:** Writing – review & editing, Validation, Investigation. **Maosong Chen:** Writing – review & editing, Validation, Investigation. **Tong Lin:** Validation, Supervision, Software, Project administration, Methodology, Formal analysis, Data curation. **Gaifeng Hu:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Conceptualization.

Declaration of competing interest

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

Acknowledgements

The authors would like to thank the International Stroke Genetics Consortium (ISGC) Intracranial Aneurysm working group for making the summary data on IA publicly available. The authors would like to thank the Mbatchou et al. and Sakaue et al. for making the summary data on serum uric acid levels publicly available.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31535.

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