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Allopurinol is Associated with an Increased Risk of Cerebral Infarction: A Two-Sample Mendelian Randomization Study

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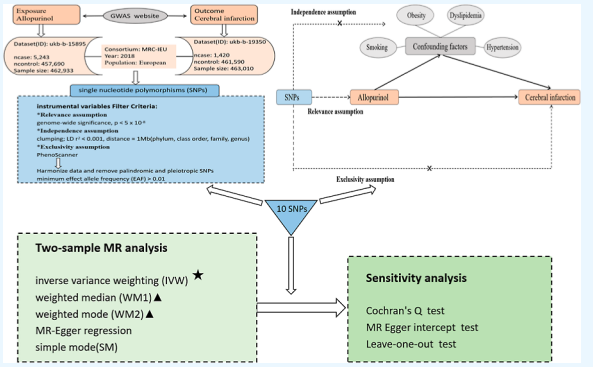
ABSTRACT: Objective: Previous studies have reported that the inappropriate use of allopurinol may increase the risk of cerebrovascular accidents, but some studies have also confirmed that allopurinol is a protective factor against stroke. To clarify whether there is a relevant causal relationship between allopurinol and cerebral infarction, we conducted a two-sample Mendelian randomization (MR) study. Methods: Data on single nucleotide polymorphisms (SNPs) associated with allopurinol and genome-wide association studies of cerebral infarction were obtained from the genome-wide association study (GWAS) web site. Five basic MR analyses were performed using MR-Egger regression, weighted median (WM1), inverse variance weighting (IVW), weighted mode (WM2), and simple mode. Sensitivity analysis was subsequently performed to detect horizontal pleiotropy, heterogeneity, and potential outliers. The final analysis results were mainly based on the IVW estimates. Results: A total of 10 SNPs were used as instrumental variables (IVs). MR analysis [(IVW: odds ratio (OR) = 1.053, 95% confidence interval (CI): 1.019−1.088, P = 0.002), (WM1: OR = 1.053, 95% CI: 1.009−1.098, P = 0.017), (WM2: OR = 1.050, 95% CI: 1.008−1.095, P = 0.044), (MR Egger: Q = 4.285, P = 0.830)] showed a positive causal association between allopurinol and the risk of cerebral infarction. Sensitivity analysis such as horizontal pleiotropy and heterogeneity increased the reliability of this result. Conclusion: The results of this study provide direct evidence that there is a causal relationship between allopurinol and cerebral infarction and that allopurinol may increase the risk of cerebral infarction.



1. INTRODUCTION

Cerebral infarction, as one of the major subtypes of stroke, is defined as severe hypoxic-ischemic tissue necrosis of the brain, often resulting in long-term functional disability and residual impairment.[1,2] Cerebral infarction is primarily caused by cerebral vascular occlusion due to embolism or thrombosis.[3] The diagnosis of cerebral infarction is typically confirmed through imaging techniques such as computed tomography and magnetic resonance imaging.[2] The risk of cerebral infarction is influenced by a number of factors including various medical conditions and lifestyle factors, such as smoking, obesity, dyslipidemia, hypertension, and diabetes mellitus, which can trigger the development of the disease.[4,5]

Our observational clinical study found that allopurinol also appears to be strongly associated with the development of cerebral infarction. Allopurinol, a xanthine oxidase inhibitor, is one of the most commonly used uric acid-lowering drugs in clinical practice.[6,7] However, several studies have shown that the use of allopurinol has some safety concerns and may have different cardiovascular effects on gout patients.[6,8] Therefore, we hypothesized that allopurinol, while widely used in the treatment of diseases such as gout, could be one of the potential risk factors for cerebral infarction.

Although several studies have analyzed the impact of genetic variations in different gene categories on ischemic stroke using various methods, such as randomized controlled trials (RCTs) or semirandomized controlled clinical trials, GRADE methodology, etc. These studies have assessed the effects of genetic variations in genes such as the apolipoprotein E (APOE) allelic variants,[5] Notch3 gene variants,[1] miR-146a gene variants,[9] and adiponectin receptor 2 gene variants[10] on cerebral infarction. However, the available studies did not provide a definitive answer as to whether there is an association between genetic abnormalities of allopurinol and the development of cerebral infarction. Therefore, the present study investigated whether there is a causal relationship between allopurinol and cerebral

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Table 1. Allopurinol of the SNPs Used as the Tool Variables[a]

SNP	Chr	position	EA	NEA	EAF	associations of allopurinol			associations of cerebral infarction		
						beta	SE	*P* value	beta	SE	*P* value
rs423144	1	155169355	T	G	0.425	−1.317 × 10−3	2.21 × 10−4	2.60 × 10−9	−1.86 × 10−4	1.16 × 10−4	0.110
rs780093	2	27742603	C	T	0.615	−2.441 × 10−3	2.25 × 10−4	1.70 × 10−27	−7.71 × 10−5	1.18 × 10−4	0.510
rs68155945	4	89270328	A	G	0.453	-1.336×10^{-3}	2.21×10^{-4}	1.50×10^{-9}	-5.11×10^{-5}	1.16×10^{-4}	0.660
rs11057184	12	122607381	G	A	0.477	-1.285×10^{-3}	2.19×10^{-4}	4.50×10^{-9}	9.43×10^{-5}	1.15×10^{-4}	0.410
rs531763	11	64352063	G	A	0.286	2.359×10^{-3}	2.42×10^{-4}	2.20×10^{-22}	1.08×10^{-4}	1.27×10^{-4}	0.400
rs1165153	6	25817789	G	A	0.567	1.907×10^{-3}	2.21×10^{-4}	5.90×10^{-18}	1.03×10^{-4}	1.16×10^{-4}	0.370
rs10774624	12	111833788	A	G	0.513	-1.249×10^{-3}	2.21×10^{-4}	1.60×10^{-8}	-9.42×10^{-5}	1.16×10^{-4}	0.420
rs10910845	1	145723120	C	A	0.535	-1.806×10^{-3}	2.20×10^{-4}	1.90×10^{-16}	-9.07×10^{-5}	1.15×10^{-4}	0.430
rs7697004	4	10028077	A	G	0.279	1.618×10^{-3}	2.44×10^{-4}	3.20×10^{-11}	2.14×10^{-4}	1.28×10^{-4}	0.094
rs938558	4	9939205	A	G	0.725	5.171×10^{-3}	2.45×10^{-4}	5.70×10^{-99}	2.68×10^{-4}	1.29×10^{-4}	0.037

[a]SNP, single-nucleotide polymorphism; Chr, chromosome; EA, effect allele; NEA, noneffect allele; EAF, effect allele frequency; Beta, estimated effect on allopurinol or cerebral infarction; SE, standard error.

infarction using Mendelian randomization (MR) analysis, with the aim of providing new evidence for research in related areas.

MR analysis is a type of analysis that uses genetic variation as an instrumental variable (IV) to test for causality.[11] The genetic basis of the method relies on the random assignment of human meiotic genes and can be used to infer plausible causal associations.[12,13] Similar to traditional randomized controlled experiments, MR analysis, examining genotypic randomized interventions using the assumptions of independence, association, and exclusivity to explore the effects of genetic variation on outcome variables through exposure factors after confounders have been excluded, provides compelling and plausible research evidence for causal hypotheses and has played a major role in studies inferring the effects of genotype on disease.[14−16] RCTs have long been considered to be the gold standard for evaluating causal relationships. However, due to factors such as high costs, lengthy duration, and limited availability of reference data, MR analysis appears to be more accessible for researchers to obtain evidence for causal hypotheses. Studies by Yin et al. and Hernán et al. have also come to the same conclusions.[12,17] In many situations where conducting RCTs is not feasible, MR may provide valuable information regarding causal relationships.[16]

In view of the above unique advantages of MR analysis, the aim of this study is to determine the causal relationship between genetic variations related to allopurinol and the occurrence of cerebral infarction using MR analysis. We believe that in-depth exploration of whether allopurinol gene polymorphisms are potential risk factors for cerebral infarction has a guiding role in the therapeutic drug bias for gout and other diseases and is also important for reducing the morbidity and mortality of cerebral infarction.

2. MATERIALS AND METHODS

2.1. Data Sources. The database related to MR analysis was obtained from the Medical Research Council Integrated Epidemiology Unit (MRC-IEU) 2018. This study was based on MR analysis to identify single nucleotide polymorphisms (SNPs) associated with allopurinol. A total of 462,933 individual data (5243 cases and 457,690 controls; European ancestry) related to allopurinol were included in the study. The genome-wide association study (GWAS) related to cerebral infarction was obtained using the GWAS web site (https://gwas.mrcieu.ac.uk/). A total of 463,010 individual data (1420 cases and 461,590 controls; European ancestry) were included in the analysis. Our study was conducted using authoritative open access databases and, therefore, did not require ethics committee approval and collection of informed consent from participants.

2.2. Research Design. The Research design is shown in the graphical abstract. The study design was based on three basic assumptions of the MR approach:[18,19] (i) genetic variation is closely associated with allopurinol; (ii) genetic variation is independent of other confounders; and (iii) genetic variation is associated with clinical outcomes only through allopurinol. The selection of allopurinol-associated SNPs during our analysis met the conventional screening criteria for instrumental variables (IVs) [$p < 5 \times 10^{-8}$, linkage disequilibrium $r^2 < 0.001$, distance 1 Mb, and the minimum effect allele frequency > 0.01].[20,21] PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner) was used to exclude SNPs that relate to confounding factors (smoking, obesity, dyslipidemia, and hypertension).[22−24] SNPs associated with allopurinol were extracted from the GWAS database by evaluating the effect of each SNPs on cerebral infarction, the effect size, and standard error and by eliminating SNPs with palindromic sequences and moderate allele frequencies.

2.3. Statistical Analysis. The exposure and outcome data sets were harmonized for analysis while ensuring that the effect allele always associated with the same allele. SNP-allopurinol and SNP-cerebral infarction estimates were then calculated using inverse variable weighting (IVW), MR-Egger regression, weighted median (WM1), weighted mode (WM2), and simple mode (SM) methods. Among them, the IVW results were used as the main reference index to assess the causal relationship between exposure and outcome in this study, and the rest of the methods were used as a supplement to the IVW assessment results. Considering the possible horizontal pleiotropy effect of IVW in causal estimation and bias by individual SNPs, we performed a series of sensitivity analyses. Cochran's Q test was used to detect whether there was significant variability between the genes in the two samples and visualized by funnel plots. Horizontal pleiotropy was detected using the MR-Egger intercept test and its corresponding 95% confidence interval (CI) to measure the bias in causal estimation due to directional pleiotropy. The stability of effect size (ES or Beta) was assessed by removing each SNP by a leave-one-out test after detecting outliers using MRPRESSO and determining its effect on other SNPs in turn. The odds ratio (OR) and corresponding 95% CI were used to quantify the strength of the causal relationship between exposure and outcome in this

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Table 2. Univariate MR Analysis of Allopurinol and Cerebral Infarction[a]

exposure/outcome	methods	NSNP	OR (95% CI)	*P* value	heterogeneity test		intercept analysis		
					Q	*P* value	intercept	SE	*P* value
allopurinol/cerebral infarction	MR Egger	10	1.049(0.979−1.125)	0.213	4.285	0.830	8.77×10^{-6}	8.01×10^{-5}	0.915
	weighted median	10	1.053(1.009−1.098)	0.017					
	IVW	10	1.053(1.019−1.088)	0.002	4.297	0.891			
	simple mode	10	1.048(0.988−1.111)	0.153					
	weighted mode	10	1.050(1.008−1.095)	0.044					

[a]MR, Mendelian-randomization; IVW, inverse-variance weighted; NSNP, number of single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; SE, standard error.

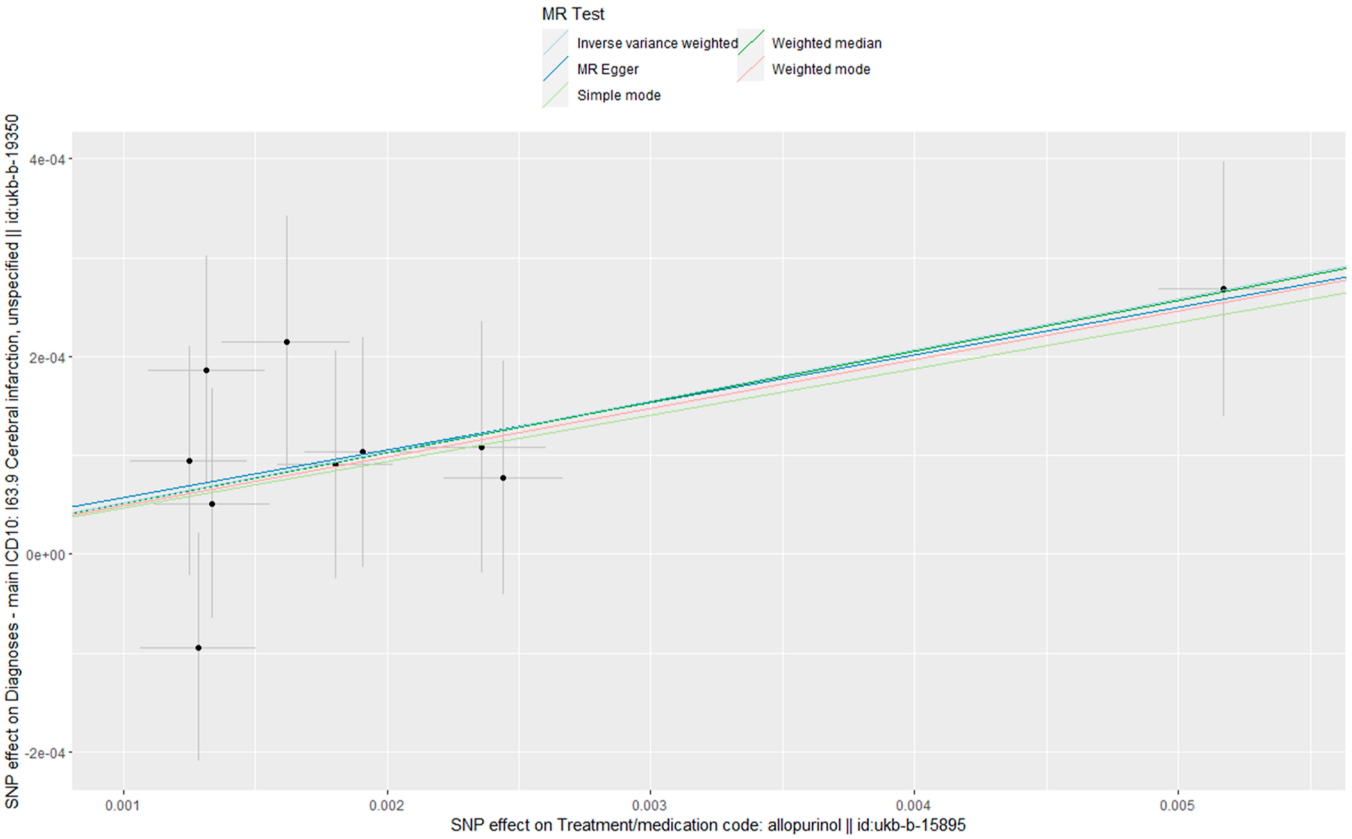

Figure 1. Scatterplot (results of MR analysis). MR, Mendelian-randomization; SNP, single-nucleotide polymorphism.

study. $P < 0.05$ was considered statistically significant. The two-sample MR (TSMR) analysis process was performed by means of "TwoSampleMR", "MRInstruments", "MRPRESSO" and "plyr" in the R 4.3.1 software.

3. RESULTS

3.1. Selection of Instrumental Variables (IVs). A total of 16 SNPs were obtained in this study (Table S1). Among them, rs7656569, rs4148155, rs13229619, rs1171614, rs73119306, and rs3747207 were excluded due to the effect of confounding factors. Ultimately, 10 SNPs were included as IVs for the analysis. Table 1 shows the details associated with these 10 SNPs.

3.2. Effect of Allopurinol on Cerebral Infarction. As shown in Table 2, the results of IVW [OR = 1.053, 95% CI: 1.019−1.088, $P = 0.002$] indicated that genetic variation in allopurinol is associated with an increased risk of cerebral infarction, which was also supported by WM1 (OR = 1.053, 95% CI: 1.009−1.098, $P = 0.017$) and WM2 (OR = 1.050, 95% CI: 1.008−1.095, $P = 0.044$). MR-Egger (OR = 1.049, 95% CI: 0.979−1.125, $P = 0.213$) and SM (OR = 1.048, 95% CI: 0.988−1.111, $P = 0.153$) results showed no statistically significant association.

3.3. Heterogeneity, Pleiotropy, and Sensitivity Analysis. Meanwhile, in the sensitivity analysis, the analysis of heterogeneity (IVW: $Q = 4.297$, $P = 0.891$) indicated that there was no significant difference between the genes of the two samples (Figure 1). The forest plot of the impact values and 95% confidence intervals estimated by the TSMR method is illustrated in Figure 2. In addition, the results of the MR Egger intercept test ($Q = 4.285$, P value = 0.830) showed that genetic pleiotropy had no significant effect on the results. The leave-one-out test showed that the robustness of the results was not affected by individual SNPs (Figure 3).

4. DISCUSSION

Based on the genome-wide association study (GWAS) database and MR analysis, we have identified a causal

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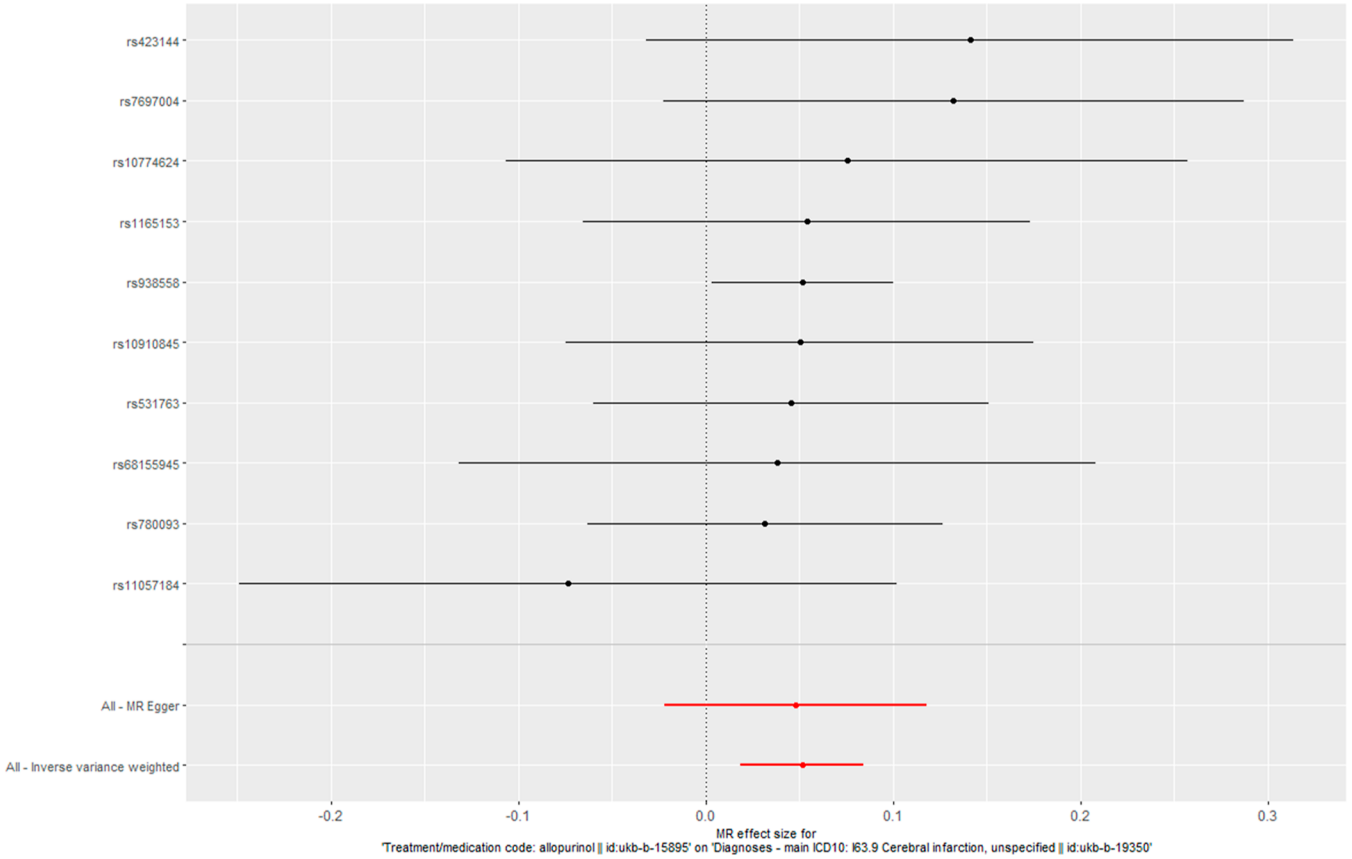

Figure 2. Forest plot (allopurinol and cerebral infarction). MR, Mendelian-randomization.

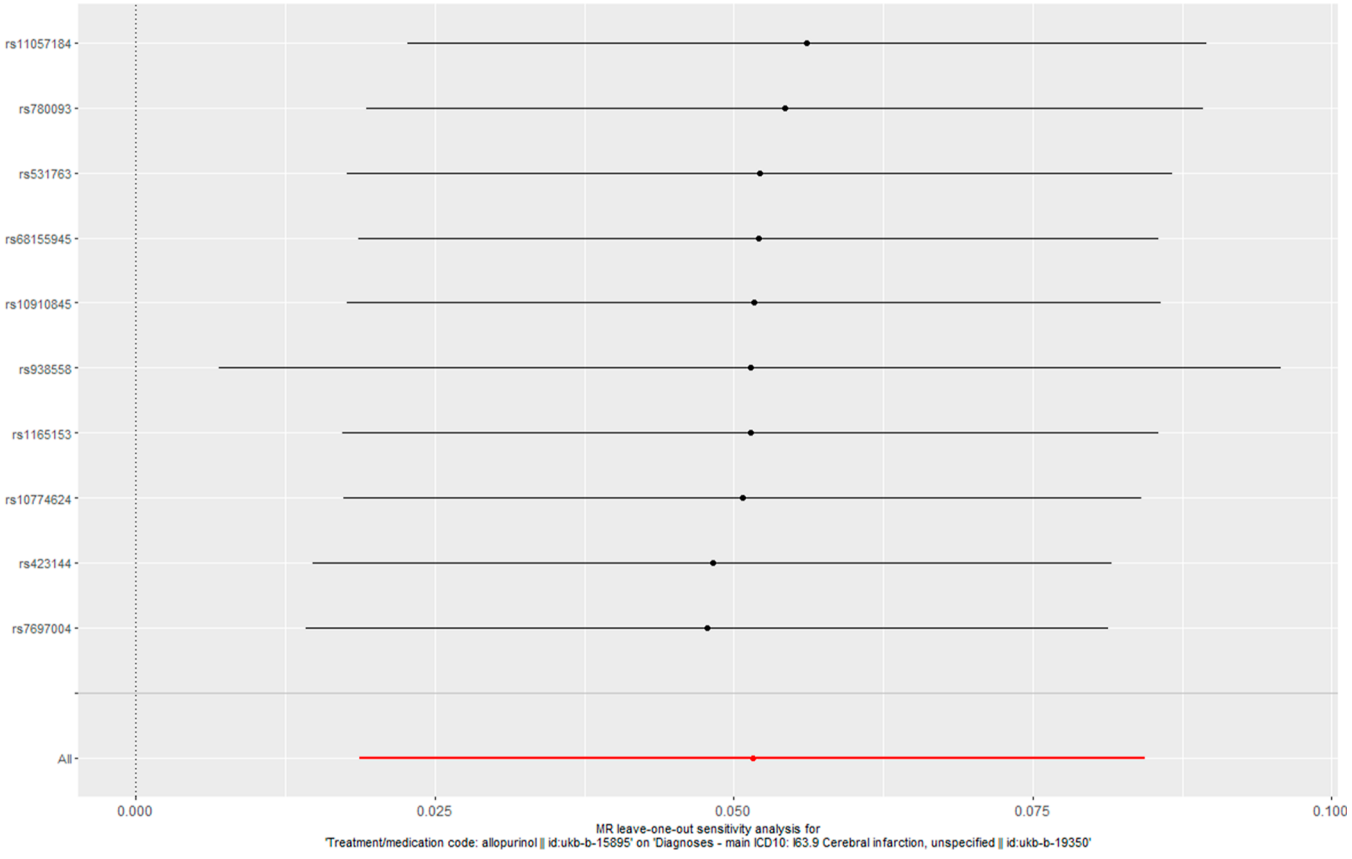

Figure 3. Sensitivity analysis (allopurinol and cerebral infarction). MR, Mendelian-randomization.

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relationship between the use of allopurinol, a commonly used therapeutic drug for gout, and the occurrence of cerebral infarction. The use of allopurinol has been found to increase the risk of cerebral infarction. MR analysis showed that the inverse variance weighting (IVW) [OR = 1.053, 95% CI: 1.019−1.088, P = 0.002], weighted median (WM1) (OR = 1.053, 95% CI: 1.009−1.098, P = 0.017), and weighted mode (WM2) (OR = 1.050, 95% CI: 1.008−1.095, P = 0.044) results all demonstrated that genetic variants of allopurinol increased the risk of cerebral infarction, but the results of MR-Egger (OR = 1.049, 95% CI: 0.979−1.125, P = 0.213) and SM (OR = 1.048, 95% CI: 0.988−1.111, P = 0.153) could not yet provide supportive evidence for our study. However, IVW is considered to be the primary and most reliable method for judging analytical results in MR analysis, while methods such as MR-Egger, WM1, and MRPRESSO are only complementary supportive evidence for the IVW method.[25] Furthermore, the OR of IVW, WM1, and MR-Egger were all greater than 1 to provide more reliable evidence for our result analysis.[26] Meanwhile, heterogeneity analysis, genetic pleiotropy, and sensitivity analysis further enhanced the credibility of our results. Therefore, we concluded that there is a positive causal relationship between allopurinol and cerebral infarction and that genetic variation in allopurinol is associated with an increased risk of cerebral infarction.

Allopurinol is a commonly used medication in clinical practice, particularly for the treatment of hyperuricemia and gout. With the improvement of people's living standards and the widespread prevalence of high-purine dietary structure, the prevalence of hyperuricemia has been increasing over the years, particularly in developing countries adopting Western lifestyles.[27−29] Hyperuricemia, in turn, is a major contributor to systemic inflammation in gout.[30] Consequently, the clinical use of allopurinol has also increased substantially.[31] A study conducted by an American nursing institution found that among the 138,724 residents evaluated, the utilization rate of allopurinol for gout treatment was as high as 60.2%.[32] Regarding the effect of allopurinol on cardiovascular and cerebrovascular, previous studies have elaborated its positive protective effects on conditions such as hypertension, coronary heart disease, myocardial infarction, and stroke while also lowering uric acid levels in patients and other indicators.[33−36] However, it has also been suggested that allopurinol use may pose potential risks and threaten people's cardiovascular and cerebrovascular health.[35,37] A systematic evaluation and meta-analysis demonstrated that allopurinol is a complex of acute coronary revascularization (OR: 0.84, 95% CI: 0.77−0.90, p < 0.001) and stroke (OR: 0.87, 95% CI: 0.79−0.97, p = 0.009), which has a strong association with the cardiovascular-related diseases.[38] This coincides with the results of our study. Consequently, the safety of allopurinol remains controversial, and its effect on cerebral infarction has not been mentioned in any studies.

During a gouty attack, elevated serum uric acid levels may promote the progression of hypertension. Improper use of allopurinol to lower uric acid levels may lead to abnormal blood pressure in patients.[39] Hypertension is a significant global health issue that affects the progression of various diseases.[40] Existing studies have shown that hypertension is one of the main factors contributing to the increased incidence of stroke.[41] Lifetime risk (LTR) is defined as the cumulative probability of developing a disease over the remaining lifespan from a given index age.[41] A cohort study by Turin et al. on cardiovascular diseases found that out of 276 participants followed up, the majority experienced ischemic stroke (166 individuals), and the stroke LTR increased with the severity of hypertension.[41]

A study conducted by Ziga and Becic selected 40 patients with hyperuricemia as subjects and statistically analyzed the uric acid values, lipid indices, and atherosclerotic index in the subjects before and after 0 and 4 months of allopurinol treatment.[7] The study demonstrated that allopurinol effectively reduced uric acid levels and improved symptoms related to gout in the treatment of hyperuricemia. However, it also significantly increased the lipid index (triglycerides, cholesterol, and LDL fraction) and atherosclerosis index in patients with metabolic syndrome (manifesting cardiovascular issues), thus becoming a risk factor for the occurrence of cardiovascular diseases.[7]

Diabetes mellitus is recognized as one of the major modifiable risk factors for stroke. In another population-based cohort study involving 2007 subjects, the LTR of stroke was 10.66% higher in diabetic men than in men without diabetes and 13.43% higher in diabetic women compared to women without diabetes. Additionally, the LTR of stroke was higher in the younger indexed age compared to the older indexed age.[42] Similar results were observed in the subtypes of cerebral infarction stroke in this study.[42] These findings highlight the significant impact of diabetes on the occurrence of stroke, particularly cerebral infarction.

Although the present study finds a direct statistically significant association between allopurinol and the risk of cerebral infarction, the underlying mechanisms by which allopurinol increases the risk of cerebral infarction are still unclear. Allopurinol, while effectively lowering uric acid levels and treating conditions such as gout, can have varying degrees of negative effects on blood pressure, blood lipids, blood glucose, and even renal function in patients. Considering the multifactorial nature of cerebral infarction, we speculate that allopurinol may directly affect cerebral vascular function or indirectly influence the risk of stroke by impacting factors such as blood pressure, blood lipids, and blood glucose levels, especially in patients with underlying conditions such as hypertension, dyslipidemia, and diabetes. Therefore, when using allopurinol in clinical practice, in addition to evaluating its positive therapeutic effects on lowering uric acid levels, a comprehensive assessment of its multifaceted impact and consideration of the patient's other disease indicators, particularly in patients with comorbidities such as hypertension, dyslipidemia, and diabetes, is crucial. The benefits and risks should be carefully weighed, and medication should be prescribed appropriately to improve patient symptoms, enhance prognosis, and reduce the incidence and mortality of cerebral infarction.

Our study still has some limitations. First, the F-value [$F = R^2(N-2)/(1-R^2)$; $R^2 = 2 \times \mathrm{EAF} \times (1-\mathrm{EAF}) \times \mathrm{beta}^2$, N is the sample size of the GWAS for the SNP-allopurinol association] is an important metric used to assess the existence of a strong correlation between the instrumental variables (IVs) and the exposure factors. However, the beta values of all 10 SNPs we identified were relatively small and all F-values were less than 10, impairing some degree of bias in the correlation between our selected IVs and the exposure factor.[43] Second, our study data were obtained solely from the GWAS database, and the sample size may be relatively limited, which could affect the completeness of our study results. Besides, our

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study noted smoking and obesity, among others, as potential confounders of cerebral infarction, but this study lacked interventions to mitigate the effects of confounders on our study sample. Some confounders that we did not notice or were unknown may also have not been excluded by us. In addition, this study found that there may be a positive causal relationship between allopurinol and cerebral infarction by MR analysis methods, but it has not been confirmed for the possible mechanism of allopurinol increasing the risk of cerebral infarction. Therefore, this will be the next research direction to which we are committed. Nevertheless, studying the effect of allopurinol on the risk of cerebral infarction is important for exploring the safety of allopurinol use. Our findings may provide evidence to further explore the safety of allopurinol and some clinical value in reducing the morbidity and mortality of cerebral infarction.

5. CONCLUSIONS

This TSMR analysis suggests that allopurinol may be a risk factor for cerebral infarction. The mechanism of action of allopurinol in increasing the risk of cerebral infarction should be further explored in the future.

■ ASSOCIATED CONTENT

Data Availability Statement

The raw data relevant to this study can be found at the following URLs: https://gwas.mrcieu.ac.uk/datasets/ukb-b-12209 and https://gwas.mrcieu.ac.uk/datasets/ukb-b-14699.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c03483.

SNPs associated with allopurinol (PDF)

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Author Contributions

[§]Equal contribution and first authorship: X.-N.M., M.-F.S., and W.F. contributed equally to this work and share first authorship. XNM, MFS, and WF performed data collection, analysis, and visualization; XNM, MFS, WF, and SLC wrote the first draft; SLC and XQZ provided software and references; CSL acquired funds and resources; and QX was responsible for the design, management, acquisition of funding and resources, and review and editing of the manuscript for this study.

Notes

The authors declare no competing financial interest.

Ethical approval: Our data were sourced from public databases and therefore do not require approval from the Ethics Committee.

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