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Uric Acid Levels and Cardiovascular and Cerebrovascular Diseases: A Mendelian Randomization Study

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Keywords
Uric acid · Cardiovascular and cerebrovascular diseases · Mendelian randomization

Abstract
Introduction: The relationship between uric acid (UA) levels and cardiovascular and cerebrovascular diseases (CCVD) is controversial. A two-sample Mendelian randomization (MR) study was conducted to explore the causal effects of UA levels on CCVD. ***Methods:*** Genetic variants strongly associated with UA levels were selected as instrumental variables from the Genome-Wide Association Study (GWAS) dataset. The GWAS data, sourced from the Global Urate Genetics Consortium (GUGC), comprised a sample size of 110,347 individuals. The selected CCVD outcomes included stroke, coronary artery disease (CAD), as well as atrial fibrillation and flutter. The primary analytical approach employed the inverse-variance weighted (IVW) method, supplemented by MR-Egger and weighted median as complementary methods. Sensitivity analysis was performed to test heterogeneity and pleiotropy. ***Results:*** The MR analysis results indicated a causal association between UA levels and stroke (odds ratio [OR]: 1.002; 95% confidence interval [CI]: 1.000–1.003; $p = 0.036$), CAD (OR: 1.118; 95% CI: 1.044–1.197; $p = 0.001$), as well as atrial fibrillation and flutter (OR: 1.141; 95% CI: 1.037–1.256; $p = 0.007$). The results of MR-Egger and weighted median methods confirmed the direction of the IVW results, enhancing the robustness of the findings. No significant anomalies were detected in the sensitivity analysis. ***Conclusion:*** The MR study suggests that UA levels exert causal effects on stroke, CAD, as well as atrial fibrillation and flutter.

Introduction

Cardiovascular and cerebrovascular diseases (CCVD) are among the leading causes of death worldwide. According to the Global Burden of Disease report, the annual loss of life due to CCVD has remained consistently high from 1990 to 2019 [1]. As a result, CCVD have been a focus in the field of chronic diseases for a long time. The risk factors associated with CCVD have received global attention.

Previous studies have shown that CCVD are influenced by many factors, including age, smoking, drinking, unhealthy diet, diabetes, hypertension, and hyperlipidemia [2–4]. Oxidative damage has also been confirmed in the pathophysiology of CCVD. Our previous research

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reported a potential relationship between low antioxidant capacity and vascular dementia, and indicated that antioxidants might reduce oxidative damage [5].

As the most abundant endogenous antioxidant in human body, uric acid (UA) has been considered to exert neuroprotective effects by clearing reactive oxygen species and nitrite [6, 7]. However, studies have shown that in certain environments, elevated levels of UA can promote oxidation and inflammation, which can lead to neuronal injury [8]. Although studies have been conducted to explore the relationship between UA levels and CCVD, no consistent conclusion has been reached [9–11].

Mendelian randomization (MR) analysis is a statistical method used in genetic epidemiology to investigate causal relationships between risk factors and diseases [12]. By leveraging the random assignment of genetic variants, MR can mimic the randomization process in a randomized controlled trial (RCT). This randomization helps to reduce confounding factors and avoid reverse causal relationships [13]. Compared to RCTs, MR studies are conducted faster and cheaper because they can use existing large-scale data for analysis [14].

At present, a two-sample MR study was conducted to estimate the causal effects of UA levels on CCVD. The outcomes observed in this study included stroke, coronary artery disease (CAD), as well as atrial fibrillation and flutter.

Materials and Methods

Study Design

A group of SNPs related to UA levels was selected from the Genome-Wide Association Study (GWAS) dataset for MR analysis to explore the association between UA levels and CCVD [15]. MR analysis is based on three key assumptions: (1) correlation assumption: SNPs should be strongly associated with exposure factors ($p < 5 \times 10^{-8}$) [14, 16, 17]; (2) independence assumption: SNPs should only affect the outcomes through the exposure factors; (3) exclusion constraint assumption: SNPs should not be associated with any confounding factors that may bias the results [18]. UA levels are considered as the exposure factor, and CCVD are considered as the outcomes of the MR study. The flowchart of the MR study is shown in online supplementary Figure S1 (for all online suppl. material, see https://doi.org/10.1159/000541624). The study methods were compliant with the STROBE-MR checklist [19], further details can be found in online supplementary Table S1. Due to the use of published research datasets that do not contain any personal identity, ethical approval is not required for this study.

Data Sources

The GWAS data for UA levels were sourced from the Global Urate Genetics Consortium (GUGC), which consisted of 110,347 individuals from 48 European cohorts accessed on February 2, 2024 [15]. The outcomes observed in this study included stroke, CAD, as well as atrial fibrillation and flutter. The GWAS data for stroke included 4,484 cases and 356,710 controls, CAD data included 60,801 cases and 123,504 controls, and atrial fibrillation and flutter data included 22,068 cases and 116,926 controls. Among the three GWAS datasets, the stroke dataset was released in 2018, the CAD dataset was released in 2015, and the atrial fibrillation and flutter dataset was released in 2021. These datasets were sourced from European research, and individuals were independent. All datasets in the study can be obtained from published articles [15, 20] or publicly available GWAS platform (https://gwas.mrcieu.ac.uk/). The detailed information of the GWAS data for stroke, CAD, as well as atrial fibrillation and flutter are shown in Table 1.

Selection Criteria of Instrumental Variables

The instrumental variables set the following criteria: (1) SNPs must be significantly correlated with UA levels ($p < 5 \times 10^{-8}$); (2) linked imbalance (LD) $r^2 < 0.001$, and index variant <10 MB; (3) SNPs directly related to the outcomes ($p < 5 \times 10^{-8}$) should be excluded; (4) SNPs that show outliers in the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test should be excluded; (5) SNPs significantly associated with CCVD risk factors in PhenoScanner should be excluded [21, 22].

Statistical Analysis

Three independent two-sample MR analyses were conducted in this study. Inverse-variance weighted (IVW) method was used as the primary analytical method, while MR-Egger and weighted median were used as supplementary methods [14]. Cochran's Q test was used to evaluate heterogeneity. MR-Egger intercept test, leave-one-out analysis and funnel plot were conducted for sensitivity analysis. $p < 0.1$ was considered as the statistical significance of the heterogeneity test, and $p < 0.05$ was considered as the statistical significance of the pleiotropy test. All statistical analyses were performed using the TwoSample MR and MR-PRESSO packages in R version 4.2.2.

Table 1. Characteristics of data sources

Traits	GWAS ID	Data publisher, publication year	Ethnicity	Sample size
Urate	ieu-a-1055	Köttgen, 2013	European	110,347
Stroke, including SAH	ukb-d-I9_STR_SAH	Neale, 2018	European	361,194
CAD	ebi-a-GCST003116	Nikpay, 2015	European	184,305
Atrial fibrillation and flutter	finn-b-I9_AF	NA, 2021	European	138,994

NA, not available.

Table 2. MR analysis of CCVD associated with UA levels

Outcome	IVW			Weighted median		MR-Egger		
	OR (95% CI)	*p*	p_{Het}	OR (95% CI)	*p*	OR (95% CI)	*p*	p_{Hor}
Stroke	1.002 (1.000–1.003)	0.036	0.794	1.002 (1.000–1.004)	0.114	1.002 (0.999–1.005)	0.177	0.776
CAD	1.118 (1.044–1.197)	0.001	0.669	1.130 (1.024–1.247)	0.015	1.111 (0.955–1.293)	0.189	0.932
Atrial fibrillation and flutter	1.141 (1.037–1.256)	0.007	0.339	1.132 (0.993–1.290)	0.065	1.117 (0.935–1.335)	0.238	0.784

CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; p_{Het}, *p* value of heterogeneity; p_{Hor}, *p* value of horizontal pleiotropy.

Results

Selection of the Instrumental Variables

In the public GWAS dataset, initially 25 SNPs were found to be significantly associated with UA levels ($p < 5 \times 10^{-8}$). These SNPs could all be found in the GWAS datasets for stroke and CAD, while 24 of these SNPs found in the GWAS dataset for atrial fibrillation and flutter. Three SNPs associated with CCVD risk factors were excluded through PhenoScanner. Specially, "*rs1260326*" was significantly associated with alcohol consumption, while "*rs642803*" and "*rs653178*" were significantly associated with hypertension. Then, 2 SNPs ("*rs11722228*" and "*rs2307394*") were removed from the analyses of CAD, and 1 SNP "*rs6598541*" was removed from the analyses of atrial fibrillation and flutter as outliers detected by the MR-PRESSO test. Finally, 22 SNPs were selected as instrumental variables for stroke, 20 SNPs for CAD, and 20 SNPs for atrial fibrillation and flutter. The detailed information of the selected SNPs is shown in online supplementary Table S2.

MR Estimates

IVW analysis results showed a causal association between UA levels and stroke (odds ratio [OR]: 1.002; 95% confidence interval [CI]: 1.000–1.003; $p = 0.036$), CAD (OR: 1.118; 95% CI: 1.044–1.197; $p = 0.001$), as well as atrial fibrillation and flutter (OR: 1.141; 95% CI: 1.037–1.256; $p = 0.007$). Furthermore, the results of MR-Egger and weighted median methods confirmed the direction of the IVW results, enhancing the robustness of the research results (Table 2 and Fig. 1).

Sensitivity Analysis

In this study, sensitivity analysis was conducted using Cochran's *Q* test, MR-Egger intercept test, leave-one-out analysis, and funnel plot to evaluate the stability of the results. As shown in Table 2, there are no significant heterogeneity and pleiotropy detected in Cochran's *Q* test or MR-Egger intercept test. Furthermore, neither leave-one-out analyses (Fig. 2) nor funnel plots (Fig. 3) detected abnormalities, indicating that the results of the study were relatively stable.

Discussion

A two-sample MR study was conducted to investigate the causal relationship between UA levels and CCVD. The MR analysis showed a causal association between UA levels and stroke, CAD, as well as atrial fibrillation and flutter, with OR values of 1.002, 1.118, and 1.141,

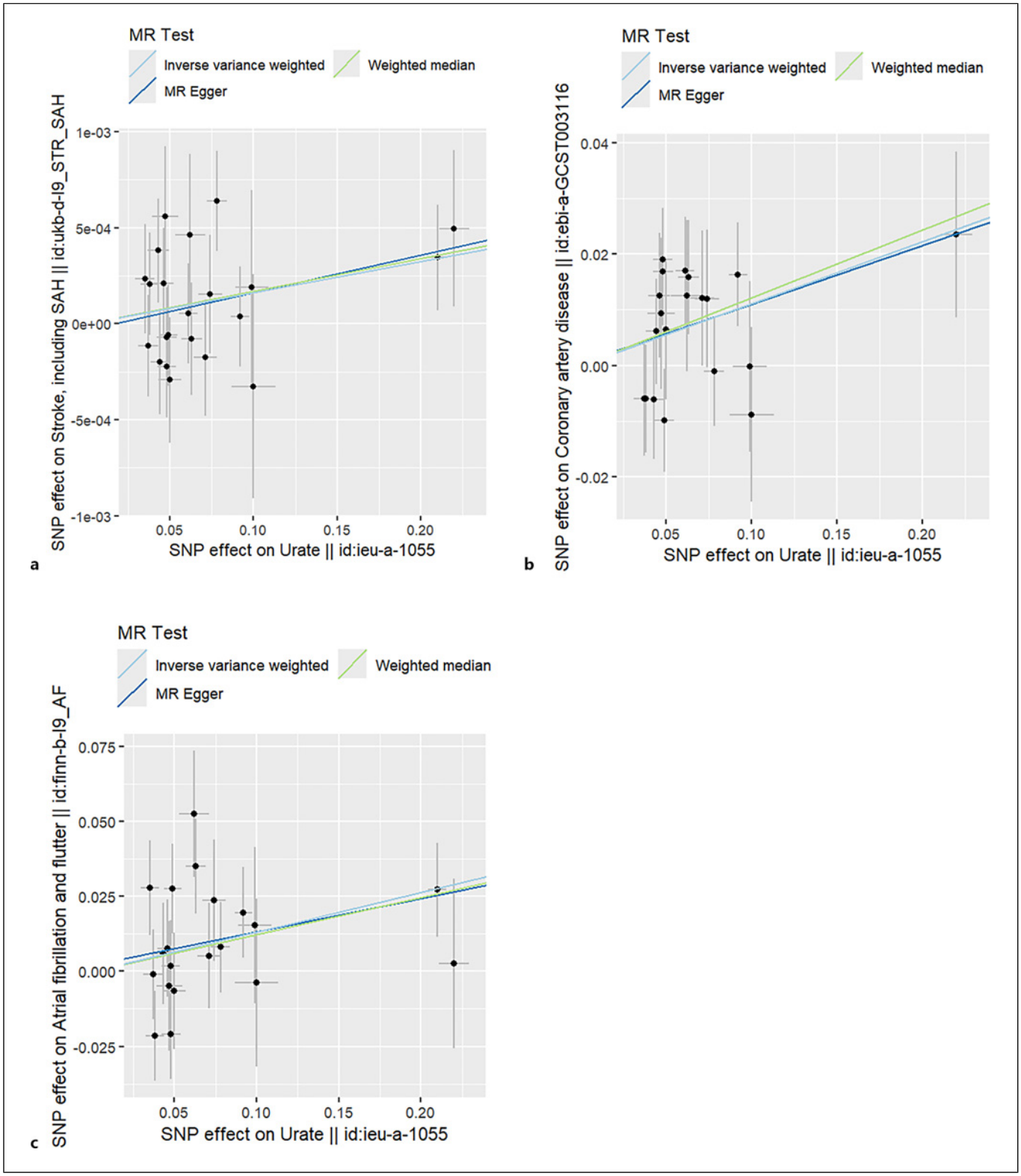

Fig. 1. Scatter plots of instrumental variable analysis results for individual single nucleotide polymorphisms and pooled estimates. **a** Stroke. **b** CAD. **c** Atrial fibrillation and flutter.

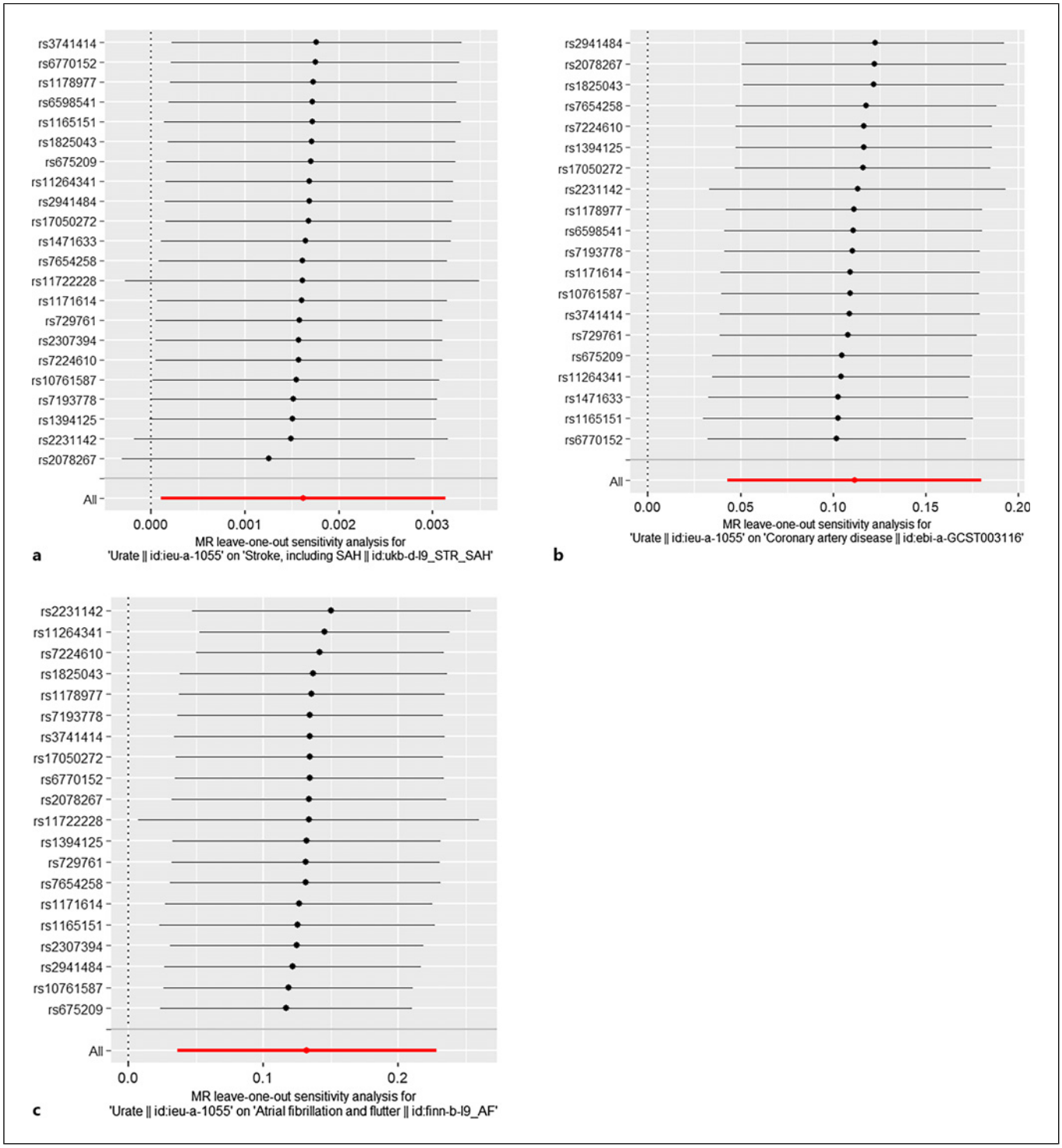

Fig. 2. Leave-one-out plots of the causal relationship between UA levels and cardiovascular and CCVD. **a** Stroke. **b** CAD. **c** Atrial fibrillation and flutter.

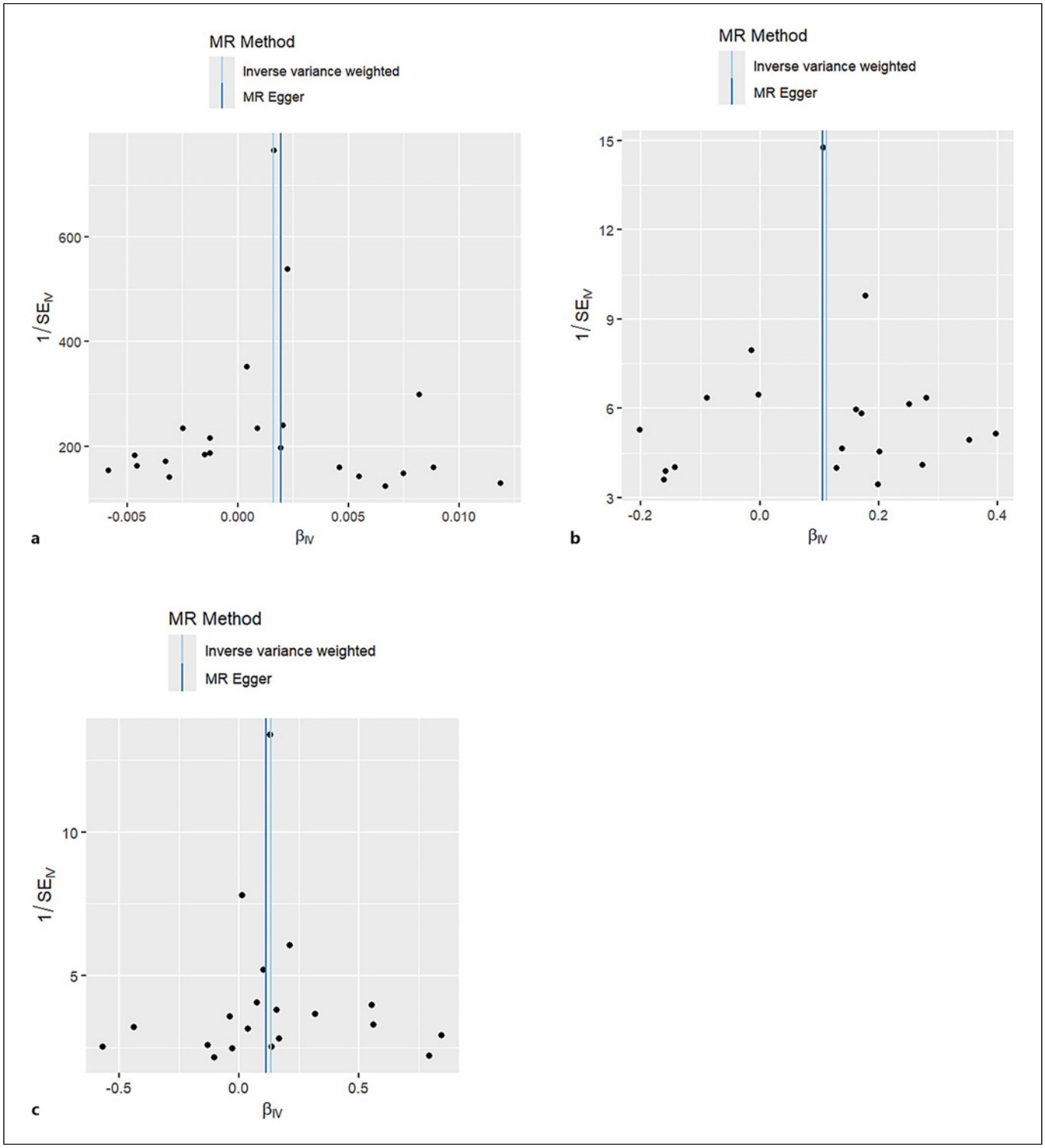

Fig. 3. Funnel plots of overall heterogeneity in MR estimation of the effect of UA levels on cardiovascular and CCVD. **a** Stroke. **b** CAD. **c** Atrial fibrillation and flutter.

respectively. The results indicated that for each unit (mg/dL) increase in UA, the risk of stroke increases by 0.2%, that of CAD by 11.8%, and that of atrial fibrillation and flutter by 14.1%. The aforementioned OR values are relatively small, possibly because they are calculated for each 1 unit change in UA. Additionally, all the p values are <0.05. Therefore, individuals with high UA levels should be given particular attention as they may be potential populations for CCVD.

Some studies have demonstrated that UA levels might be associated with CCVD [23–25]. Dong et al. [24] have conducted a dose-response meta-analysis to explore the relationship between UA levels and the risk of stroke. The research results indicated that high UA levels could increase the risk of stroke, with a nonlinear dose-response relationship. Li et al. [25] have conducted a prospective cohort study of 123,238 Chinese patients to explore the association between UA levels and the risk of atrial fibrillation. They found that elevated UA levels might increase the potential risk of atrial fibrillation. However, some studies have shown that UA, as an indicator of the body's redox homeostasis, can alleviate nerve damage and exert neuroprotective effects [26, 27]. We have just conducted a meta-analysis to explore the association between UA levels and vascular dementia and Parkinson's disease dementia. The meta-analysis results indicated that UA levels were associated with Parkinson's disease dementia, but not with vascular dementia, which helped to strengthen our knowledge of the role of UA in the pathophysiology of diseases [28].

UA has been reported to be associated with various CCVD risk factors, such as obesity, insulin resistance, and metabolic syndrome [29–31]. Although the relevant mechanism between CCVD and UA levels is not clear, studies have shown that UA is a product of xanthine oxidoreductase, which is one of the important processes of reactive oxygen species in the body. Elevated UA levels may be a sign of upregulation of xanthine oxidoreductase activity or increased oxidative stress [32, 33]. Therefore, high levels of UA may indicate oxidative damage to cells, ultimately resulting in CCVD.

Some RCTs have been conducted to evaluate the effectiveness of targeted interventions in reducing and preventing CCVD. Evidence has suggested that therapies that reduce UA levels can lower blood pressure in adolescents with hyperuricemia and improve endothelial function in patients with heart failure [34, 35]. However, Givertz et al. [36] have found that although xanthine oxidase inhibition with allopurinol could reduce UA levels, failed to improve clinical status, or left ventricular ejection fraction at 24 weeks. The present MR study indicates that UA levels exert causal effects on stroke, CAD, as well as atrial fibrillation and flutter. This suggests therapies that reduce UA levels may reduce the risk of stroke, CAD, as well as atrial fibrillation and flutter. To further confirm it, larger sample size RCTs are needed.

Some limitations of this study should be pointed out. First, the results of MR-Egger and weighted median were not entirely consistent with the IVW method. Since IVW method is the most efficient (with highest statistical power), the estimated results of IVW are preferentially used [14]. Second, since our MR study is limited to the European population, the conclusion in the study may be not suitable for other populations. Therefore, caution is necessary when drawing conclusions. Besides, it would be of great interest to explore the causal relationships on other populations. Third, although sensitivity analysis did not detect significant pleiotropy, the presence of horizontal pleiotropy cannot be completely ruled out, and residual pleiotropy may still lead to biased results. Moreover, although the results of the relationship between UA and CCVD are statistically significant, the practical significance still needs further exploration due to the small OR values. Despite the limitations, the MR analysis reduced the impact of confounding factors and provided a more reliable assessment of the causal relationship between UA levels and CCVD. The results of MR-Egger and weighted median methods confirmed the direction of the IVW results, indicating the robustness of the findings. Additionally, the sensitivity analysis did not detect any anomalies, further supporting the reliability of the results.

Conclusions

UA levels have causal effects on stroke, CAD, as well as atrial fibrillation and flutter. The findings are expected to promote the development of prevention and treatment strategies for CCVD, indicating that the regulation of UA levels may be beneficial in both preventing and treating stroke, CAD, as well as atrial fibrillation and flutter. Further studies are required to validate the causal relationship.

Acknowledgments

We are appreciative of all the participants in this study.

Statement of Ethics

No ethical approval or informed consent was necessary because this study is based on publicly accessible databases.

Conflict of Interest Statement

All authors have agreed to the manuscript submission and confirm that the work has not been submitted simultaneously to another journal for consideration. In addition, all authors declare no conflicts of interest.

Author Contributions

Xiaowen Hou designed the study, wrote the first draft, and revised the manuscript. Kaiwen Cen, Yunfeng Zhu, and Zhi Zhu conducted the data analysis. Zhiyu Zhang and Xu Feng collected the data. All authors contributed to the article and approved the submitted version.

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Data Availability Statement

All data used in the study were obtained from published articles or publicly available GWAS platform (https://gwas.mrcieu.ac.uk/).

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