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Causal relationship between serum uric acid and cardiovascular disease: A Mendelian randomization study

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ABSTRACT

Background: Observational studies have established an association between serum uric acid and cardiovascular disease (CVD). However, these studies are susceptible to uncontrolled confounders and reverse causality bias. To overcome these challenges, we employed a two-sample Mendelian randomization (MR) approach to investigate the causal link between serum uric acid and CVD.

Methods: We utilized Genome-wide association study (GWAS) data for serum uric acid and six CVD: coronary artery disease (CAD), hypertension, myocardial infarction (MI), heart failure (HF), angina, and coronary heart disease (CHD). MR analyses employed inverse variance weighting (IVW), MR-Egger, weighted median, and weighted model. Sensitivity analyses were conducted to assess result reliability, including Cochrane's Q test, MR-Egger intercept, MR-PRESSO, and the leave-one-out approach.

Results: IVW analysis revealed that a genetic predisposition to elevated serum uric acid levels significantly increases the risk of CVD, with higher odds ratios (ORs) observed for CAD (OR: 1.227; 95 % CI: 1.107–1.360, $P = 0.0002$), hypertension (OR: 1.318, 95 %CI: 1.184–1.466, $P = 2.13E-06$), MI (OR: 1.184, 95 %CI: 1.108–1.266, $P = 2.13E-06$), HF (OR: 1.158, 95 %CI: 1.066–1.258, $P = 2.13E-06$), angina (OR: 1.150, 95 %CI: 1.074–1.231, $P = 0.0002$) and CHD (OR: 1.170, 95 %CI: 1.072–1.276, $P = 0.0005$). Sensitivity analysis research results have robustness.

Conclusion: This MR study robustly demonstrates a significant causal relationship between genetically elevated serum uric acid and various cardiovascular diseases, suggesting that higher levels may enhance the risk of cardiovascular events. Consequently, patients with elevated uric acid levels warrant early and aggressive interventions to mitigate cardiovascular risks.

1. Introduction

Cardiovascular disease (CVD) is a pathology affecting the heart and blood vessels, encompassing conditions like hypertension, coronary heart disease, myocardial infarction, and heart failure [1]. As the global population ages, the incidence of CVD has been progressively increasing. According to the World Health Organization, CVD is the leading cause of mortality among non-communicable diseases, claiming approximately 17.8 million lives annually, which constitutes one-third of global deaths. This trend significantly threatens human life and health [2,3]. Therefore, understanding the factors influencing the development of cardiovascular diseases is crucial for their early prevention, diagnosis, and treatment.

Uric acid is considered a biologically inactive waste product resulting from purine metabolism, and it was identified as the cause of gout [4]. Many Observational studies have linked uric acid with increased incidence and mortality rates of CVD, which might contribute to CVD through inflammatory responses, oxidative stress, Renin-Angiotensin System (RAS) activation, and endothelial dysfunction [5–7]. Chen et al. [8] indicated that patients with high uric acid levels face a 1.5 to 3.0 times greater risk of CVD compared to those with normal levels. In a cohort study that included 25,284 Chinese people, Tian et al. [9] found that the risk of cardiovascular disease increased with elevated uric acid levels in individuals without hyperuricemia or other traditional cardiovascular disease risk factors. However, observational studies are inherently limited by reverse causation and confounding factors, leading

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to potential bias that obscures the true relationship. Meta-analyses of the effects of uric acid on cardiovascular disease provide estimates of the increased risk of cardiovascular disease, Miao et al. [10] showed that Serum uric acid is positively associated with the risk of adverse events in chronic heart failure patients. Zuo et al. [11] found that uric acid levels were prognostically associated with coronary heart disease mortality, with a 9 % increase in mortality for every 1 mg/dL increase in uric acid. The studies evaluated in the *meta*-analysis can introduce bias to the findings due to the high risk of bias in the quality assessment section and the different thresholds for high and low uric acid in different studies. And, similar to observational studies, a causal relationship could not be fully established. Therefore, the causal relationship between uric acid levels and CVD remains unknown, and it is important to reveal the potential impact of uric acid levels on the initiation of CVD and its progression, which will help to reduce the risk of CVD by monitoring and regulating uric acid levels.

Mendelian randomization (MR) is an analytical method employing single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to assess causal relationships between exposures and outcomes [12]. As genetic variants are assigned randomly at conception, MR circumvents confounding factors and reverse causality, common issues in traditional observational studies [13–14]. In this study, we used two-sample MR analysis to investigate the causal relationship between serum uric acid and cardiovascular disease (CVD), contributing novel insights for CVD prevention.

2. Materials and methods

2.1. Study design

We conducted a two-sample MR analysis using public GWAS summary data (https://gwas.mrcieu.ac.uk/). In this analysis, serum uric acid was considered the "exposure", while coronary artery disease (CAD), hypertension, myocardial infarction (MI), heart failure (HF), angina, and coronary heart disease (CHD) were the "outcomes." This approach evaluated the causal relationship between serum uric acid levels and CVD. We assessed heterogeneity through Cochran's Q test and verified causality reliability using sensitivity analyses, including pleiotropy and "leave-one-out" analyses. Informed consent and ethical approval were obtained in the original publications and publicly available databases. The MR Analysis rested on three critical assumptions: (1) IVs are strongly associated with serum uric acid levels. (2) There is no association between IVs and confounding factors. (3) IVs influence CVD solely through serum uric acid (Fig. 1).

2.2. Data sources

Our systematic analysis utilized GWAS summary statistics from a comprehensive cohort to determine a causal link between serum uric acid and CVD. The serum uric acid dataset (GWAS ID: ebi-a-GCST90018977) comprised 343,836 participants with 19,041,286 SNPs. The analysis included six CVDs: CAD (42,096 cases and 361 controls), hypertension (55,917 cases and 162,837 controls), MI (14,825 cases and 44,000 controls), HF (47,309 cases and 93,0014 controls), angina (30,025cases and 440,906 controls) and CHD (60,801 cases and 123,504 controls). To minimize population heterogeneity bias, only aggregated data from European populations were included. For detailed information on the GWAS dataset, refer to Table 1.

2.3. Selection of the instrumental variables (IVs)

To elucidate the causal relationship between serum uric acid and seven CVDs, we identified IVs for serum uric acid. In this study, single nucleotide polymorphisms (SNPs) were selected as IVs based on the

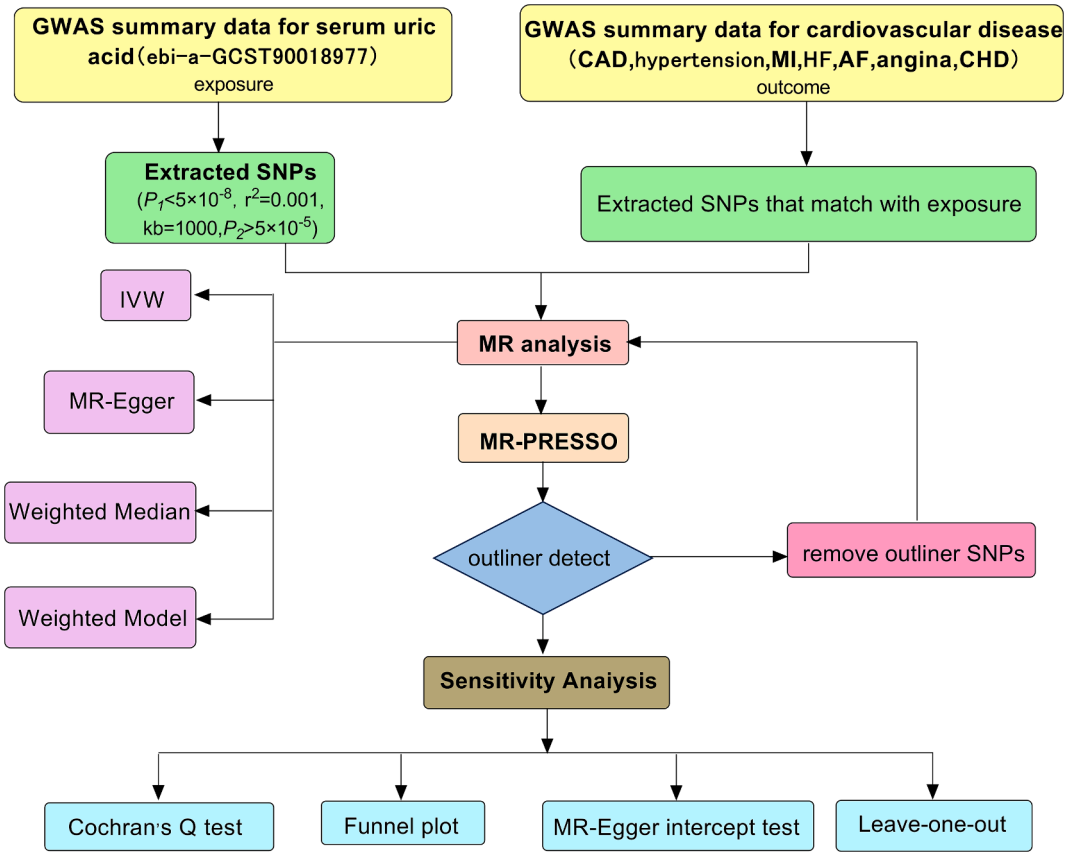

Fig. 1. Flow chart of the MR Study between serum uric acid and 6 cardiovascular diseases.

Table 1
Summary of serum uric acid and cardiovascular disease gwas dataset.

Trait	GWAS ID	Participants	nSNPs	PMID	Ethnicity
serum uric acid	ebi-a-GCST90018977	343,836 individuals	19,041,286	34,594,039	European
coronary artery disease	ebi-a-GCST003116	42,096 cases and 361 controls	8,597,751	26,343,387	European
hypertension	finn-b-I9_HYPTENS	55,917 cases and 162,837 controls	16,380,466	NA	European
myocardial infarction	ebi-a-GCST011365	14,825 cases and 44,000 controls	8,106,745	33,532,862	European
heart failure	ebi-a-GCST009541	47,309 cases and 930,014 controls	7,773,021	31,919,418	European
angina	ebi-a- GCST90018793	30,025 cases and 440,906 controls	470,931	34,594,039	European
coronary heart disease	ieu-a-7	60,801 cases and 123,504 controls	9,455,779	26,343,387	European

following criteria: (1) SNPs significantly associated with serum uric acid ($P < 5 \times 10^{-8}$) were extracted [15]; (2) To ensure SNP independence, those in linkage disequilibrium (LD) ($r^2 = 0.0001$, kb = 10000) were excluded [16]; (3) SNPs closely related to the seven CVD were eliminated ($P > 5 \times 10^{-5}$) [17]; (4) SNPS that were missing or palindromic with moderate allele frequency were removed from the outcome data [18]; (5) The F statistic was calculated for each SNP to assess weak instrumental variable influence, discarding those with F < 10 [19]. $F=\frac{R^2(n-2)}{1-R^2}$, where n is the exposure sample size, and R^2 is the proportion of variation in the exposure database explained by SNPs. R^2 is calculated as follows: $R^2 = 2\times$ (1-MAF) $\times$ (MAF $\times \beta^2$) where MAF is the minor allele frequency and β is the allele effect value; (6) SNPs associated with potential confounders (BMI, blood lipid level, diabetes, alcohol consumption) were identified and removed using the PhenoScanner V2 database (https://www.phenoscanner.medschl.cam.ac.uk/) [20]; (7) An MR-PRESSO outlier test was conducted to eliminate anomalous SNP [21]. Subsequently, MR Analysis was performed with the included SNPs.

2.4. Mendelian randomization (MR) analysis

Four distinct methods were employed to estimate the causal effect between serum uric acid and CVD: inverse variance weighting (IVW), MR-Egger, weighted median (WM), and weighted model [22]. These methods address varying levels of horizontal pleiotropy, thereby thoroughly assessing the causal relationship between serum uric acid and CVD: (1) IVW, assuming no horizontal pleiotropy among SNPs, amalgamates Wald ratio estimates from each SNP to yield a combined causality estimate with optimal statistical power [23]; (2) MR-Egger accounts for the presence of horizontal pleiotropy and provides consistent results under the Instrument Strength Independent of Direct Effect (InSIDE) assumption [24]; (3) WM aggregates data from multiple genetic variants into a singular causal estimate, offering consistent effect estimation even if up to 50 % of the data originates from invalid IVs [25]; (4) The weighted model assigns causal estimates to each genetic variant inversely proportional to its variance [26]. Thus, IVW analysis serves as the primary MR method, complemented by the other three techniques to enhance result reliability. Additionally, we applied False Discovery Rate (FDR) correction, establishing statistical significance at an adjusted P-value threshold of 0.05.

2.5. Sensitivity analysis

To ensure a robust MR Estimate, several sensitivity analyses were conducted:

The Cochran's Q test, applied to both the IVW and MR-Egger methods, assessed heterogeneity. A P-value greater than 0.05 indicated an absence of heterogeneity. Additionally, potential heterogeneity was visually appraised using funnel plots [27]. (2) The MR-Egger-intercept test evaluated horizontal pleiotropy, with P > 0.05 suggesting no such pleiotropy [21]. (3) A leave-one-out analysis was performed by sequentially excluding each SNP to determine if a single SNP biased the IVW estimate results [28].

2.6. Statistical analysis

All analyses were conducted using R software (version 4.3.0), employing the "Two-Sample-MR" (version 0.5.6), "MR-PRESSO" (version 1.2), and "MendelianRandomization" (version 0.4.3) R packages for Mendelian randomization.

3. Results

3.1. Identification of instrumental variables (IVs)

A comprehensive description of all SNPs used in this study is presented in Supplementary Table 1. All SNPs met the established screening criteria. The selected SNPs exhibited F statistics above 10, indicating no weak tool bias and robustly predicting the causal effect of serum uric acid on CVD in MR Analyses.

3.2. Causal effects of serum uric acid on cardiovascular diseases

Fig. 2 illustrates the genetic association between serum uric acid and various cardiovascular diseases. The primary analysis using the IVW method revealed that genetically predicted serum uric acid increases the risk of cardiovascular diseases, including CAD (OR: 1.155; 95 % CI: 1.074–1.242, $P = 0.0002$), hypertension (OR: 1.318, 95 %CI: 1.184–1.466, $P = 2.13E-06$), MI (OR: 1.184, 95 %CI: 1.108–1.266, $P = 2.13E-06$), HF (OR: 1.158, 95 %CI: 1.066–1.258, $P = 2.13E-06$), angina (OR: 1.150, 95 %CI: 1.074–1.231, $P = 0.0002$) and CHD (OR: 1.170, 95 %CI: 1.072–1.276, $P = 0.0005$). Complementary MR statistical models, including MR-Egger, weighted median, and weighted model, yielded effect estimates directionally consistent with the IVW approach.

3.3. MR sensitivity analysis

The results of the sensitivity analysis are presented in Table 2. Cochran's Q test revealed no heterogeneity among SNPs in the analysis of CAD's causal effect ($Q\_pval_{IVW} = 0.2095$, $Q\_Pval_{MR\text{-}Egger} = 0.2099$), leading to the use of a fixed-effect IVW model for analysis. Conversely, in analyses of other causal effects, including hypertension($Q\_pval_{IVW} = 6.35E-31$,$Q\_pval_{MR\text{-}Egger} = 2.52E-30$), MI ($Q\_pval_{IVW} = 1.64E-05$, $Q\_pval_{MR\text{-}Egger} = 1.35E-05$), HF ($Q\_pval_{IVW} = 1.23E-07$, $Q\_pval_{MR\text{-}Egger} = 9.64E-08$), angina ($Q\_pval_{IVW} = 3.69E-24$, $Q\_pval_{MR\text{-}Egger} = 7.50E-24$), and CHD ($Q\_pval_{IVW} = 1.50E-08$, $Q\_pval_{MR\text{-}Egger} = 1.17E-08$), heterogeneity among SNPs was observed, necessitating the use of a random-effects IVW model for analysis. Furthermore, the symmetry of the points represented by each SNP in the funnel plot corresponded to the results of Cochran's Q test (Supplementary Fig. 1).

Employing the MR-Egger intercept test, we evaluated whether genetic variations related to serum uric acid could contribute to CVD through alternative pathways. The results, as shown in Table 3, indicate no horizontal pleiotropy in our MR analysis ($P > 0.05$), suggesting that the study's conclusions are stable and reliable (Supplementary Fig. 2). Furthermore, the leave-one-out approach reveals that the inferred causal relationship between serum uric acid and CVD risk is not attributable to any single SNP (Supplementary Figure 3).

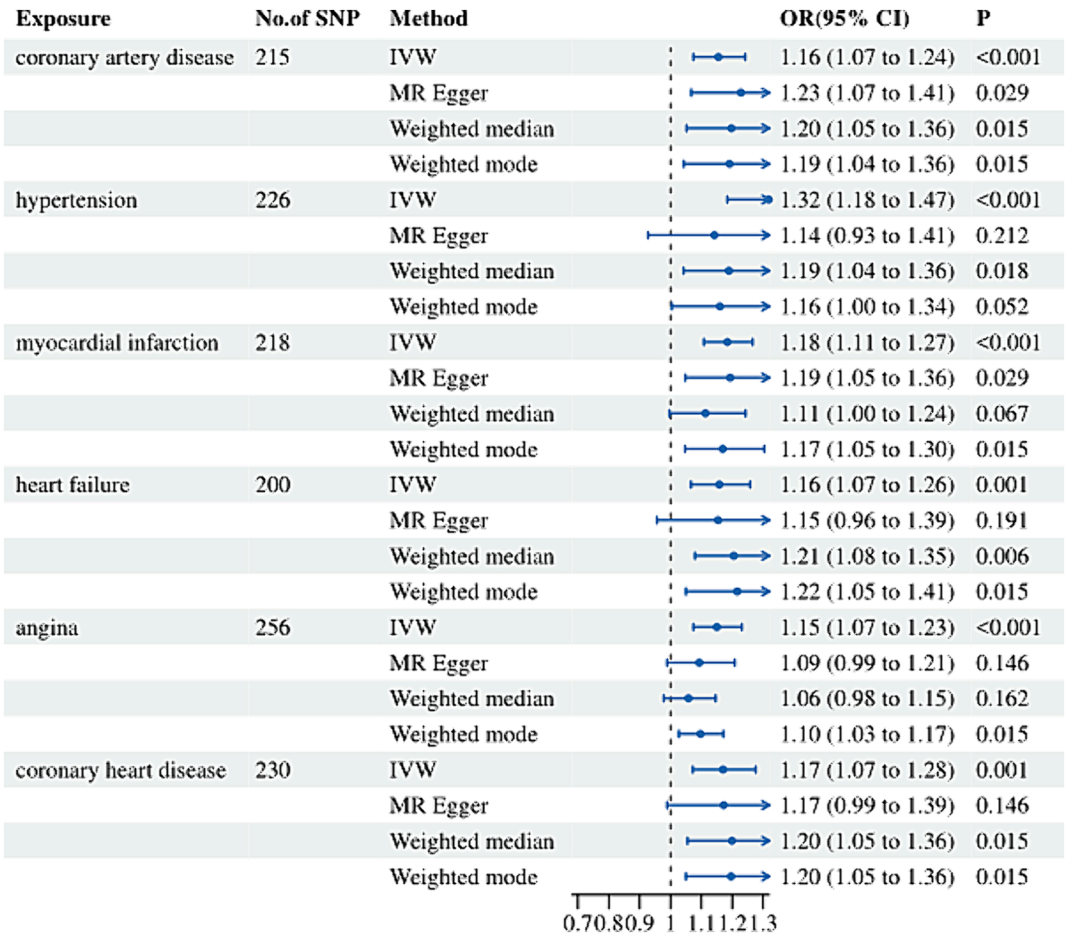

Fig. 2. Forest plot of MR analysis results serum uric acid and cardiovascular diseases.

Table 2
The results of heterogeneity analysis for serum uric acid on cardiovascular diseases.

Traits (outcome)	Methods	*Q*	Q-dif	*P*
coronary artery disease	IVW	230.4616	213	0.209488
	MR-Egger	229.392	214	0.209892
hypertension	IVW	563.0569	225	6.35E-31
	MR-Egger	566.9734	224	2.52E-30
myocardial infarction	IVW	314.5666	217	1.64E-05
	MR-Egger	314.5448	216	1.35E-05
heart failure	IVW	319.5367	199	1.23E-07
	MR-Egger	319.5343	198	9.46E-08
angina	IVW	553.5222	255	3.69E-24
	MR-Egger	549.4822	254	7.50E-24
coronary heart disease	IVW	368.0202	229	1.50E-08
	MR-Egger	368.0195	228	1.17E-08

Table 3
MR-Egger intercept analysis of horizontal pleiotropy between serum uric acid and cardiovascular disease.

Traits (outcome)	Egger_Intercept	se	*P*
coronary artery disease	−0.00157	0.001571	0.320091
hypertension	0.0036	0.002301	0.119187
myocardial infarction	−0.00018	0.001442	0.902801
heart failure	7.53E-05	0.001944	0.969163
angina	0.00186	0.001361	0.172972
coronary heart disease	−4.02E-05	0.001863	0.982812

4. Discussion

We conducted a two-sample MR analysis using four analytical methods to evaluate the causal relationship between genetically predicted serum uric acid and CVD. Our findings indicate a causal association between higher serum uric acid levels and an increased risk of CAD, hypertension, MI, HF, angina, and CHD. The sensitivity analysis demonstrated the absence of horizontal pleiotropy, affirming the robustness of the effect estimates and confirming that none of the instrumental variables significantly influenced the outcome variables. Therefore, early detection and management of high serum uric acid are crucial in preventing the onset and progression of cardiovascular diseases.

Given the widespread prevalence of hyperuricemia and the high incidence of CVD globally, understanding the role of hyperuricemia in CVD is crucial. Numerous observational studies over recent decades have indicated an association between uric acid and increased risk of CVD outcomes. In our Mendelian Randomization (MR) analysis, we specifically examined the causal relationship between serum uric acid and six prevalent types of CVD. Kleber et al. [29] reported that each 1 mg/dl increase in uric acid raised the risk of CVD mortality by 0.77 times. Kojima et al. [30], utilizing the Japanese Acute Coronary Syndrome Research Database to assess 1,124 patients, found that the mortality rate in acute myocardial infarction (MI) patients with low uric acid levels was only a quarter of that in the high uric acid group. A study involving 21,386 participants identified elevated uric acid as an independent risk factor for HF [31]. Research in the general elderly female population revealed that uric acid levels exceeding 404.6 μmol/L tripled the risk of hypertension [32]. A cohort study of 16,063 Chinese patients

showed a 14 % increase in the risk of CHD in middle-aged and elderly individuals for every 100 μmol/L increase in serum uric acid levels [33]. Ma et al. [34] found higher uric acid levels in patients with angina compared to a control group. These findings align with our MR analysis, suggesting uric acid as a contributing risk factor in the development of CVD.

There are multiple potential mechanisms explaining the causal link between serum uric acid and CVD. High uric acid levels can lead to the formation of urate crystals, depositing in vascular endothelium and causing endothelial damage through oxidative stress. This process activates platelets and increases blood viscosity, potentially resulting in local thrombosis [35]. Uric acid can also exacerbate the oxidation of low-density lipoprotein, lipid peroxidation, and the production of oxygen free radicals. This stimulates the adherence of white blood cells to endothelial cells, initiating an oxidative stress response. The uptake of uric acid by endothelial cells can rapidly induce nuclear factor-kappa B (NF-κB) activation, stimulating chemokine and adhesion factor production, and promoting mononuclear cell migration and adherence to endothelial cells, ultimately leading to atherosclerosis [36]. Normal endothelial function, crucial for maintaining vasoconstriction and diastolic stability, is impaired by elevated uric acid levels, which can reduce nitric oxide (NO) availability, resulting in vascular endothelial dysfunction [37].

Our research has several advantages. Firstly, the sample size of this study significantly exceeds that of prior observational studies, thereby providing ample statistical power. Secondly, we employed five MR analysis methods and conducted sensitivity analyses, where the consistency of results across these methods enhanced the study's credibility. Finally, compared with previous MR Studies, we used MR to analyze the causal association between serum uric acid and 6 types of CVDs in the study design. More stringent criteria were used to screen SNPs associated with serum uric acid, which not only excluded SNPS associated with confounders, but also used "MR-PRESSO" to remove outlier SNPS. To ensure authenticity of the findings, we used an adjusted P value $<$ 0.05 as a condition for a causal association between serum uric acid and cardiovascular disease.However, this study also has limitations: (1) All data were derived from the European population, which, while reducing bias due to racial differences, limits the generalizability of the results. Further studies are needed with corresponding GWAS datasets for other ethnic groups; (2) The data from the GWAS database are aggregated statistics, lacking individual-level detail, thus precluding statistical subgroup analysis; (3) Heterogeneity among SNPs may introduce bias into the study results. Nonetheless, the use of a random effects model in our study makes this heterogeneity acceptable [38].

In conclusion, this study systematically explored the potential causal relationship between serum uric acid and six types of CVD using a two-sample MR approach. The findings suggest that serum uric acid is a risk factor for CVD, indicating that correcting high serum uric acid levels may help prevent the onset of CVD. Therefore, further in vivo and in vitro experiments are necessary to understand the complex interplay between serum uric acid and CVD and to elucidate its underlying biological mechanisms, with the aim of reducing the incidence and prevalence of CVD.

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CRediT authorship contribution statement

Yujun Zhang: Data curation. **Qiufang Lian:** Supervision. **Yanwu Nie:** Methodology. **Wei Zhao:** Software.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101453.

References

[1] C.W. Tsao, A.W. Aday, Z.I. Almarzooq, et al., Heart disease and stroke statistics-2022 update: a report from the American heart association, Circulation 145 (2022) e153–e639, https://doi.org/10.1161/CIR.0000000000001052.
[2] GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. (2017) 390:1151-1210. doi: 10.1016/ S0140-6736(17)32152-9.
[3] G.A. Roth, G.A. Mensah, C.O. Johnson, et al., Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study, J. Am. Coll. Cardiol. 76 (2020) 2982–3021, https://doi.org/10.1016/j.jacc.2020.11.010.
[4] P. Strazzullo, J.G. Puig, Uric acid and oxidative stress: relative impact on cardiovascular risk? Nutr Metab Cardiovasc Dis 17 (6) (2007) 409–414, https://doi.org/10.1016/j.numecd.2007.02.011.
[5] Y. Luo, Q. Wu, R. Meng, et al., Associations of serum uric acid with cardiovascular disease risk factors: a retrospective cohort study in southeastern China, BMJ Open 13 (2023) e073930.
[6] N. Katsiki, M. Kouvari, D.B. Panagiotakos, et al., The association between serum uric acid levels and 10-year cardiovascular disease incidence: results from the ATTICA prospective study, Rev. Cardiovasc. Med. 22 (2021) 991–1001, https://doi.org/10.31083/j.rcm2203108.
[7] C. Borghi, D. Agnoletti, A.F.G. Cicero, E. Lurbe, A. Virdis, Uric acid and hypertension: a review of evidence and future perspectives for the management of cardiovascular risk, Hypertension 79 (2022) 1927–1936, https://doi.org/10.1161/HYPERTEN SIONAHA.122.17956.
[8] J.H. Chen, S.Y. Chuang, H.J. Chen, W.T. Yeh, W.H. Pan, Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study, Arthritis Rheum. 61 (2009) 225–232, https://doi.org/10.1002/art.24164.
[9] X. Tian, P. Wang, S. Chen, et al., Association of normal serum uric acid level and cardiovascular disease in people without risk factors for cardiac diseases in China, J. Am. Heart Assoc. 12 (2023) e029633.
[10] L. Miao, M. Guo, D. Pan, et al., Serum uric acid and risk of chronic heart failure: a systematic review and meta-analysis, Front Med (Lausanne) 8 (2021) 785327, https://doi.org/10.3389/fmed.2021.785327.
[11] T. Zuo, X. Liu, L. Jiang, S. Mao, X. Yin, L. Guo, Hyperuricemia and coronary heart disease mortality: a meta-analysis of prospective cohort studies, BMC Cardiovasc. Disord. 16 (2016) 207, https://doi.org/10.1186/s12872-016-0379-z.
[12] B. Zuo, S. Zhu, G. Zhong, H. Bu, H. Chen, Causal association between placental growth factor and coronary heart disease: a Mendelian randomization study, Aging (Albany NY) 15 (2023) 10117–10132, https://doi.org/10.18632/aging.205061.
[13] S. Burgess, G. Davey Smith, N.M. Davies, et al., Guidelines for performing Mendelian randomization investigations: update for summer 2023, Wellcome Open Res. 4 (2023) 186, https://doi.org/10.12688/wellcomeopenres. 15555.3.
[14] G. Huang, X. Chen, Y. Chen, et al., Causal relationship between type 2 diabetes mellitus and bone mineral density: a Mendelian randomization study in an East Asian population, Osteoporos Int. 34 (2023) 1719–1727, https://doi.org/10.1007/s00198-023-06807-6.
[15] S. Burgess, D.S. Small, S.G. Thompson, A review of instrumental variable estimators for Mendelian randomization, Stat. Methods Med. Res. 26 (2017) 2333–2355, https://doi.org/10.1177/0962280215597579.
[16] G. Hemani, J. Zheng, B. Elsworth, et al., The MR-Base platform supports systematic causal inference across the human phenome, Elife 7 (2018) e34408.
[17] A.G. Hoek, S. van Oort, P.J.M. Elders, J.W.J. Beulens, Causal association of cardiovascular risk factors and lifestyle behaviors with peripheral artery disease: a Mendelian randomization approach, J. Am. Heart Assoc. 11 (2022) e025644.
[18] Q. Feng, A.J. Grant, Q. Yang, et al., Genetically predicted vegetable intake and cardiovascular diseases and risk factors: an investigation with Mendelian randomization, Nutrients 15 (2023) 3682, https://doi.org/10.3390/nu15173682.
[19] S. Burgess, S.G. Thompson, Avoiding bias from weak instruments in Mendelian randomization studies, Int. J. Epidemiol. 40 (2011) 755–764, https://doi.org/10.1093/ije/dyr036.

[20] M. Li, C. Jiang, Y. Lai, et al., Genetic evidence for causal association between atrial fibrillation and dementia: a Mendelian randomization study, J. Am. Heart Assoc. 12 (2023) e029623.
[21] M. Verbanck, C.Y. Chen, B. Neale, R. Do, Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases, Nat. Genet. 50 (2018) 693–698, https://doi.org/10.1038/s41588-018- 0099-7.
[22] D.A. Lawlor, R.M. Harbord, J.A.C. Sterne, N. Timpson, S.G. Davey, Mendelian randomization: using genes as instruments for making causal inferences in epidemiology, Stat. Med. 27 (2008) 1133–1163, https://doi.org/10.1002/sim.3034.
[23] J. Bowden, M.F. Del Greco, C. Minelli, G. Davey Smith, N. Sheehan, J. Thompson, A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization, Stat. Med. 36 (2017) 1783–1802, https://doi.org/10.1002/sim.7221.
[24] J. Bowden, G. Davey Smith, S. Burgess, Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression, Int. J. Epidemiol. 44 (2015) 512–525, https://doi.org/10.1093/ije/dyv080.
[25] N. Gao, M. Ni, J. Song, M. Kong, D. Wei, A. Dong, Causal relationship between tea intake and cardiovascular diseases: a Mendelian randomization study, Front. Nutr. 9 (2022) 938201, https://doi.org/10.3389/fnut.2022.938201.
[26] S. Burgess, J. Bowden, T. Fall, E. Ingelsson, S.G. Thompson, Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants, Epidemiology 28 (2017) 30–42, https://doi.org/10.1097/EDE.0000000000000 559.
[27] J. Bowden, M.F. Del Greco, C. Minelli, et al., Improving the accuracy of two-sample summary-data Mendelian randomization: moving beyond the NOME assumption, Int. J. Epidemiol. 48 (2019) 728–742, https://doi.org/10.1093/ije/dyy258.
[28] J. Bowden, W. Spiller, M.F. Del Greco, et al., Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the Radial plot and Radial regression, Int. J. Epidemiol. 47 (4) (2018) 1264–1278, https://doi.org/10.1093/ije/dyy101.
[29] M.E. Kleber, G. Delgado, T.B. Grammer, et al., Uric acid and cardiovascular events: a Mendelian randomization study, J Am Soc Nephrol 26 (2015) 2831–2838, https://doi.org/10.1681/ASN.2014070660.
[30] S. Kojima, T. Sakamoto, M. Ishihara, et al., Prognostic usefulness of serum uric acid after acute myocardial infarction (the Japanese Acute Coronary Syndrome Study), Am. J. Cardiol. 96 (2005) 489–495, https://doi.org/10.1016/j.amjcard.2005.04.007.
[31] M.L. Muiesan, M. Salvetti, A. Virdis, et al., Serum uric acid, predicts heart failure in a large Italian cohort: search for a cut-off value the URic acid Right for heArt Health study, J. Hypertens. 39 (2021) 62–69, https://doi.org/10.1097/HJH.0000000000002589.
[32] A. Mazza, S. Lenti, L. Schiavon, et al., Asymptomatic hyperuricemia is a strong risk factor for resistant hypertension in elderly subjects from general population, Biomed. Pharmacother. 86 (2017) 590–594, https://doi.org/10.1016/j.biopha.2016.11.104.
[33] X. Lai, L. Yang, S. Légaré, et al., Dose-response relationship between serum uric acid levels and risk of incident coronary heart disease in the Dongfeng-Tongji Cohort, Int. J. Cardiol. 224 (2016) 299–304, https://doi.org/10.1016/j.ijcard.2016.09.035.
[34] Q.Q. Ma, X.J. Yang, N.Q. Yang, et al., Study on the levels of uric acid and high-sensitivity C-reactive protein in ACS patients and their relationships with the extent of the coronary artery lesion, Eur. Rev. Med. Pharmacol. Sci. 20 (2016) 4294–4298.
[35] Y. Saito, A. Tanaka, K. Node, Y. Kobayashi, Uric acid and cardiovascular disease: a clinical review, J. Cardiol. 78 (2021) 51–57, https://doi.org/10.1016/j.jjcc.2020.12.013.
[36] W.Y. Liang, X.Y. Zhu, J.W. Zhang, X.R. Feng, Y.C. Wang, M.L. Liu, Uric acid promotes chemokine and adhesion molecule production in vascular endothelium via nuclear factor-kappa B signaling, Nutr. Metab. Cardiovasc. Dis 25 (2015) 187–194, https://doi.org/10.1016/j.numecd.2014.08.006.
[37] C. Gersch, S.P. Palii, K.M. Kim, A. Angerhofer, R.J. Johnson, G.N. Henderson, Inactivation of nitric oxide by uric acid, Nucleosides Nucleotides Nucleic Acids 27 (2008) 967–978, https://doi.org/10.1080/15257770802257952.
[38] Y. Wang, Y. Zhang, C. Zhao, W. Cai, Z. Wang, W. Zhao, Physical activity, sedentary behavior, and osteoarthritis: a two-sample Mendelian randomization analysis, Iran. J. Public Health 52 (2023) 2099–2108, https://doi.org/10.18502/ijph.v52i10.13848.