Nutrition, Metabolism & Cardiovascular Diseases (2024) **34**, 1008–1013

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Uric acid levels and heart failure: A mendelian randomization study

Jiaqi Zheng [a,1], Kaiwen Cen [a,1], Jiajun Zhang [a], Huan Zhang [b], Mingguang Zhao [c], Xiaowen Hou [a,*]

[a] School of Public Health, Shenyang Medical College, Shenyang, 110034, China
[b] Officers' Ward Department, General Hospital of Northern Theater Command, Shenyang, 110034, China
[c] Department of Neurosurgery, General Hospital of Northern Theater Command, Shenyang, 110034, China

Received 7 September 2023; received in revised form 18 November 2023; accepted 24 December 2023
Handling Editor: Claudio Borghi
Available online 30 December 2023

KEYWORDS
Uric acid;
Heart failure;
Mendelian randomization;
Causal effects

Abstract *Background and aims:* Uric acid, the end-product of purine metabolism within the human body, has been the subject of studies exploring its potential association with cardiovascular and cerebrovascular diseases. However, the precise relationship between uric acid levels and heart failure remains elusive.
Methods and results: In this particular study, aggregated data from genome-wide association studies on uric acid and heart failure were utilized to perform a two-sample Mendelian randomization (MR) analysis utilizing R software. The aim was to uncover any causal link between these variables. The primary outcome was assessed using inverse variance weighted (IVW) methodology, while sensitivity analyses employed MR-Egger, weighted median (WME), and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) techniques. IVW results revealed a possible causal relationship between elevated uric acid levels and an increased risk of heart failure (OR: 1.09, 95 % CI: 1.01–1.17, $P < 0.05$). Encouragingly, the directions provided by MR-Egger and WME aligned with IVW findings, and no anomalies were detected in the remaining sensitivity analyses.
Conclusion: These outcomes indicate the stability of the results of the study, thereby suggesting that heightened uric acid levels may contribute to an augmented risk of heart failure.

1. Introduction

Heart failure manifests as a syndrome characterized by indicators and symptoms of cardiac insufficiency, leading to a reduction in life expectancy [1]. Numerous factors may contribute to the development of heart failure, with smoking, obesity, hypertension, diabetes, coronary artery disease, and genetics being the most prevalent risk factors [2]. Statistics reveal that over 64 million individuals worldwide presently endure heart failure, with a prevalence of 1–2% among adults in developed nations [3]. Due to its impact on global public health, addressing the health concerns associated with heart failure through the identification of predictive markers or risk factors becomes crucial for human well-being.

Uric acid, stemming from purine metabolism, serves as an antioxidant within the human body and aids in maintaining blood pressure [4]. However, when uric acid is present in the cell cytoplasm or the acidic/hydrophobic environment of atherosclerotic plaques, it transforms into a pro-oxidant that fuels oxidative stress. Through this mechanism, uric acid becomes involved in the pathophysiological processes of coronary heart disease (CHD) [5].

* Corresponding author. School of Public Health, Shenyang Medical College, 146 Huanghe North Street, Shenyang, 110034, China.
E-mail address: sophia_hxw@163.com (X. Hou).
[1] The first 2 authors contributed equally to this work.

https://doi.org/10.1016/j.numecd.2023.12.023

Additionally, serum uric acid closely correlates with obesity, hypertension, dyslipidemia, glucose metabolism disorders, and metabolic syndrome, amongst others [6]. Given that heart failure represents the advanced stage of most cases of coronary heart disease, which exhibits close associations with hypertension, myocardial infarction, atrial fibrillation, and valvular disease, some scholars propose that uric acid may play a significant role in heart failure. Relevant studies have shown that increased serum uric acid levels may serve as a critical risk factor for the occurrence and prognosis of heart failure [7]. Nevertheless, research exploring the relationship between uric acid and heart failure remains relatively scarce, with controversy surrounding their connection. By employing Mendelian randomization (MR) in this study, the study aims to delve into the association between uric acid and heart failure, thus offering fresh insights for the clinical management of heart failure.

A novel approach was presented by MR to causal inference in epidemiological investigations by leveraging hypothesized additional genetic variants that adhere to the instrumental variable (IV) hypothesis [8]. The validity of MR Results is determined by the validity of three hypotheses (relevance hypothesis, independence hypothesis, and exclusivity hypothesis), which necessitate individual examination by researchers based on their expertise.

Randomized controlled trials (RCTs) represent the gold standard for establishing causal relationships between exposures and specific outcomes, making them an essential component of medical research endeavors [9]. However, challenges are often confronted by RCTs related to resource-intensive requirements in terms of manpower, material resources, and time. In the absence of feasible RCTs, MR serves as a strategy that simulates RCTs, providing evidence for causal inference. Over recent years, MR has gained widespread adoption within medical research as a promising methodology for assessing causality.

In summary, this study employs aggregated data from genome-wide association studies (GWAS) to conduct MR analysis, exploring the causal relationship between uric acid and heart failure. The overarching objective is to furnish evidence-based medicine that can inform the prevention and treatment of heart failure, ultimately contributing to improved well-being.

2. Methods

2.1. Study design

Within this study, two-sample MR analysis is utilized to investigate the causal connection between uric acid levels and heart failure. Firstly, single nucleotide polymorphisms (SNPs) associated with uric acid levels are sourced from the GWAS database. Subsequently, data pertaining to heart failure associations were obtained, and qualified SNPs were meticulously selected to elucidate the instrumental variables employed in this study. Finally, MR, along with a series of statistical analyses, comprehensively evaluated the causal relationship between uric acid levels and heart failure. Ethical approval specific to this experiment was not required.

Furthermore, this MR design adhered to the following three hypotheses: (1) Instrumental variables exhibit significant correlation with exposure factors (relevance hypothesis); (2) The instrumental variables remain independent of potential confounding factors influencing the exposure-outcome relationship (independence hypothesis); (3) Instrumental variables solely impact outcomes through exposure (exclusivity hypothesis).

2.2. Data source

Exposure and outcome data for this study were derived from publicly available IEU Open GWAS summary data. The exposure-related GWAS data encompassed 110,347 individuals from 48 European cohorts, with mean serum urate concentrations ranging from 3.9 to 6.1 mg/dl (median 5.2 mg/dl) across all cohorts. The data comprised information on 4,865,122 SNPs obtained from the Global Urate Genetics Consortium (GUGC). More detailed data can be found in Kottgen's original article [10]. In this GWAS meta-analysis, 37 independent loci demonstrated associations with serum urate concentration at a significance threshold ($P < 1 \times 10^{-6}$), with 26 of these loci exhibiting significant associations ($P < 5 \times 10^{-8}$). Outcome-related GWAS data, publicly accessible in 2021, incorporated 13,087 cases and 192,618 controls across European populations, involving 16,380,466 SNPs. Notably, all sample data within this study were independent from one another.

2.3. Selection criteria for instrumental variables

Instrumental variables in this study were screened based on the following criteria. Inclusion criteria: (1) SNPs displaying genome-wide significance in relation to serum urate levels ($P < 5 \times 10^{-8}$); (2) Linkage disequilibrium (LD) $r^2 < 0.001$, kb < 10000. Exclusion criteria: (1) SNPs associated with outcome ($P < 5 \times 10^{-6}$); (2) SNPs associated with significant factors impacting the potential risk of heart failure, as per the PhenoScanner website (http://www.phenoscanner.medschl.cam.ac.uk/) ($P < 5 \times 10^{-8}$); (3) SNPs exhibiting anomalies in MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis.

2.4. Statistical analysis

In this study, random effects model was adapted for data consolidation, employing three MR analysis methods: inverse variance weighted (IVW), MR-Egger, and weighted median (WME). A significance level of $P < 0.05$ was considered statistically significant. IVW served as the primary method for results, while MR-Egger and WME were employed to assess the consistency of direction and further verify the findings. IVW combined causal effect estimates from Wald ratios obtained from different SNPs using meta-analysis when each genetic variable satisfies the assumption of one instrumental variable, thereby providing a summary estimate of the causal effect of

exposure on outcome [11]. MR-Egger accounted for horizontal pleiotropy by incorporating the MR-Egger intercept. WME allowed for inclusion of invalid instruments under the assumption that at least half of instruments employed in MR analysis were valid.

Sensitivity analyses consisted of MR-PRESSO, Cochran's Q test, MR-Egger intercept assessment, leave-one-out analysis, and funnel plot. Cochran's Q test was utilized to evaluate the heterogeneity within this study. MR-PRESSO, MR-Egger intercept test, leave-one-out analysis, and funnel plot were employed to test for pleiotropy. When MR-PRESSO results indicate the presence of outliers, the MR analysis requires reexecution after excluding said outliers.

Additionally, the power of the results, representing the degree of confidence, was calculated. Firstly, the sum of sample size, proportion of cases, OR, and R^2 of SNPs was extracted. Secondly, this study utilized mRnd: Power calculations for Mendelian Randomization website (https://shiny.cnsgenomics.com/mRnd/) to perform the calculation.

All aforementioned analyses were conducted using R software.

3. Results

3.1. Selection of instrumental variables

Following a series of quality control measures, 24 SNPs associated with uric acid were initially included. Upon consulting the PhenoScanner website, two SNPs significantly linked to heart failure risk factors ($P < 5 \times 10^{-8}$) were eliminated, namely "rs1260326" associated with alcohol consumption and "rs3184504" associated with diabetes. Consequently, 22 SNPs were ultimately utilized as instrumental variables. Specific information was shown in Table S1. The F-value statistics for all SNPs surpass 10, indicating minimal potential for weak instrumental variable bias within this study.

3.2. Statistical analysis

The IVW results demonstrated a possible causal relationship between elevated uric acid levels and increased risks of heart failure (OR: 1.09, 95%CI: 1.01−1.17, $P < 0.05$). The other two MR methods also exhibited consistent directions with IVW. Cochran's Q test and MR-Egger intercept test indicated the absence of heterogeneity and horizontal pleiotropy in this study ($P > 0.05$). Detailed MR analysis results were shown in Table S2, Fig. 1, and Fig. 2. No outliers were detected via MR-PRESSO ($P > 0.05$). Leave-one-out analysis (Fig. 3) and funnel plot (Fig. 4) exhibited no abnormalities. Additionally, the test power of these results were determined to be 0.80, thereby affirming the stability and reliability of the outcomes.

4. Discussion

This study employed a two-sample Mendelian randomization (MR) approach to investigate the causal relationship between uric acid levels and heart failure. Three MR analysis methods were utilized, with inverse variance weighted (IVW) as the primary outcome, and MR-Egger and weighted median (WME) used for consistency evaluation and result validation. The findings of this study supported the notion that elevated uric acid levels may heighten risks of heart failure. Furthermore, sensitivity analyses detected no anomalies, indicating the stability and reliability of results. Overall, this study contributed new insights into the association between uric acid and heart failure, while providing evidence-based medical knowledge for the prevention and treatment of this condition.

In terms of observational data on the relationship between uric acid and heart failure, Keenan's team came up with the opposite result, using a similar MR analysis for causal assessment of serum urate levels in cardiometabolic diseases, including heart failure, which covered 4,526 cases and 18,400 controls [12]. The results did not support the causal role of serum uric acid levels in heart failure. However, other researchers have arrived at the same conclusion as our study. In the multicenter, nationwide Italian cohort study of 21,386 individuals, uric acid was identified as an independent risk factor for both all heart failure and fatal heart failure after adjusting for potential confounding variables. The study showed that prognostic cutoff values for uric acid levels could be determined, with the values > 5.34 mg/dl indicating an increased risk of all heart failure, and the values > 4.89 mg/dl indicating an increased risk of fatal heart failure [13]. An epidemiological study examining data from the adult population of the United States between 2007 and 2016, comprising 17,349 individuals, demonstrated an association between elevated serum uric acid concentration and heart failure risk [14]. Huang et al. conducted a meta-analysis of 5 studies and found that for every 1 mg/dl increase in serum uric acid, the risk of heart failure increased by 19 % [15].

Although the precise mechanism underlying the association between uric acid levels and heart failure remains unclear, it has been observed that increased uric acid levels were associated with adverse hemodynamic characteristics in heart failure patients, including higher right atrial pressure and pulmonary capillary wedge pressure, higher pulmonary artery pressure and pulmonary vascular resistance index, as well as lower cardiac index, indicating an association between uric acid levels and vascular tension and cardiac function [16]. Cicero et al. reported an inverse correlation between serum uric acid and cardiac output and stroke volume [17]. Moreover, uric acid may contribute to pathophysiological processes of heart failure and cardiovascular disease by promoting oxidative stress and inflammation [18]. Despite numerous studies exploring the potential mechanisms linking uric acid to heart failure, the issue remains controversial and requires verification through extensive clinical studies in the future.

The only previous MR study examining the relationship between uric acid and heart failure, conducted by Keenan et al., was published in 2016 [12]. One advantage of our study was inclusion of a larger number of heart failure patients, approximately three times the number of cases in

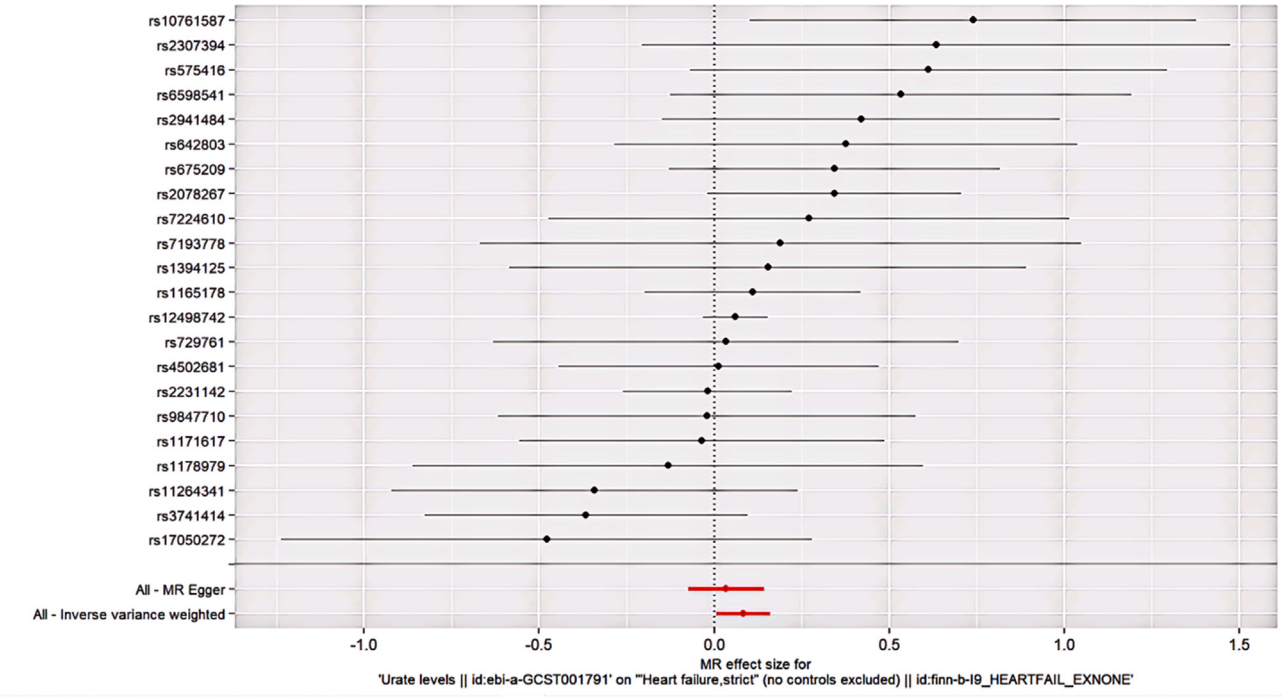

Figure 1 Forest plot of the causal effect of uric acid-related SNPs on heart failure.

the aforementioned study, which enhanced the statistical power. Furthermore, the GWAS data on heart failure employed in our study were generated in 2021, making it more up-to-date with current research standards.

These significant strengths lied in large sample size, including 13,087 heart failure patients, and utilization of SNPs from 22 independent loci. Additionally, calculated test power for this experiment was 0.80, signifying an 80 %

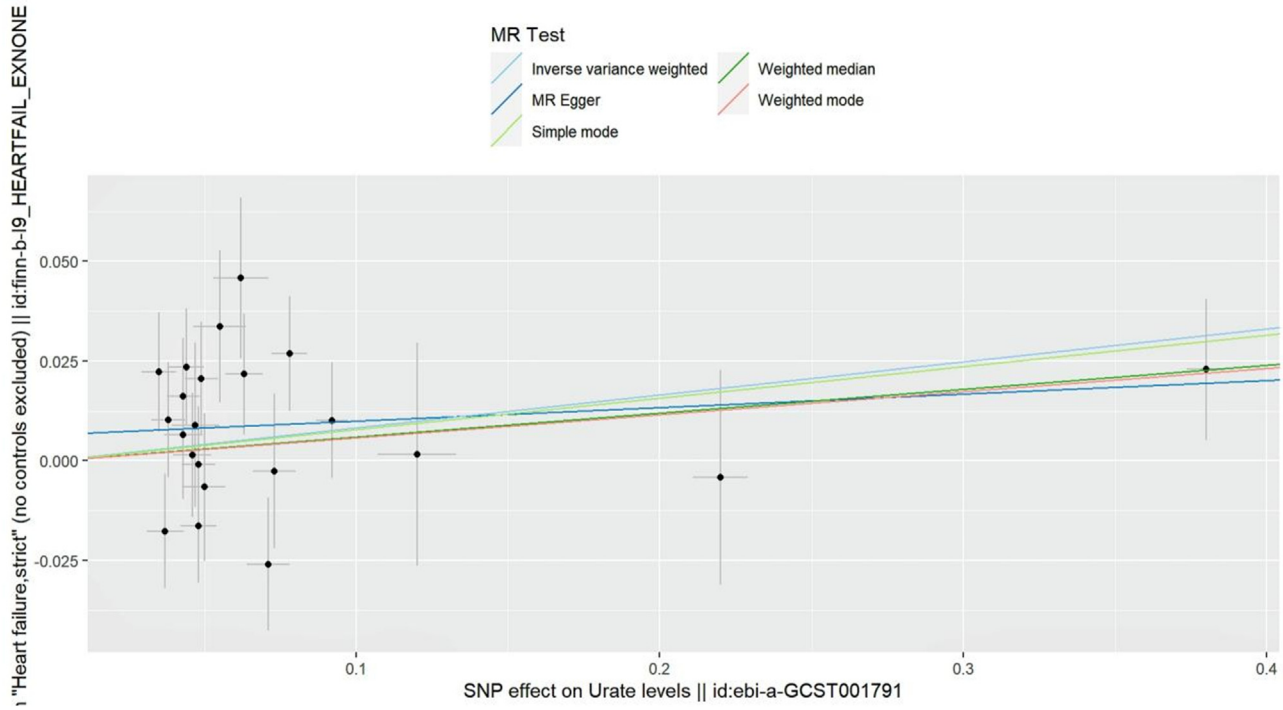

Figure 2 Scatter plot of uric acid-related SNPs associated with heart failure.

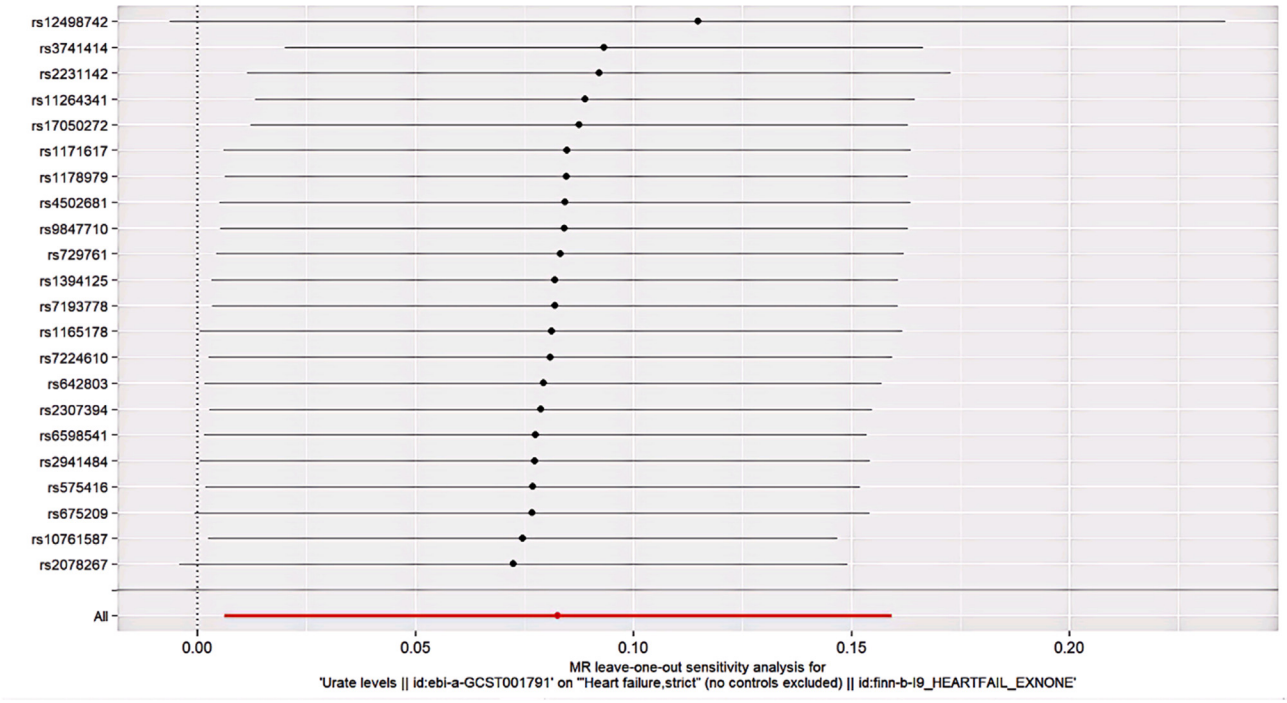

Figure 3 Leave one out analysis plot of effect of uric acid levels on heart failure.

confidence level that elevated uric acid levels may increase risks of heart failure. Moreover, genetic variants were employed as instrumental variables, and sample data originated from European populations, thereby reducing confounding biases inherent in previous observational studies.

When exploring the relationship between uric acid levels and heart failure, it's crucial to take into account the influence of renal function and diuretic therapy. Both renal dysfunction and diuretic therapy can lead to the elevated levels of uric acid, which are confounding variables that may affect the relationship between uric acid levels and heart failure [19,20]. Furthermore, acute coronary syndrome is probably associated with high uric acid levels, which is considered as another potential

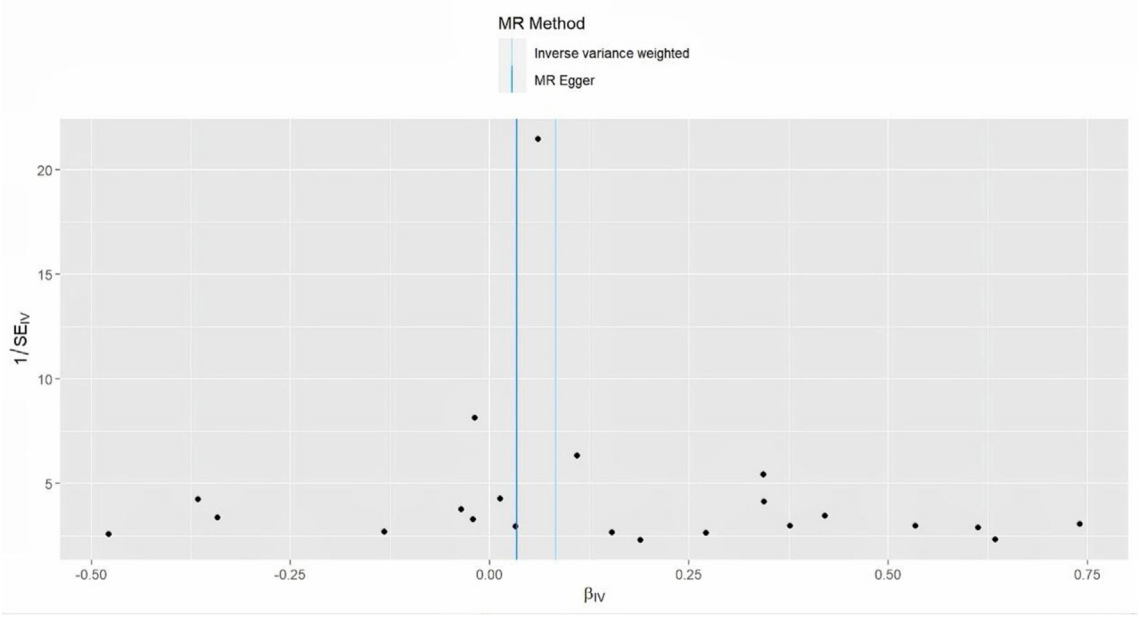

Figure 4 Funnel plot of effect of uric acid levels on heart failure.

confounding factor [21]. Unfortunately, the data we obtained did not include information on renal function, diuretic therapy or acute coronary syndrome. In order to reliably explore the relationship between uric acid levels and heart failure, renal function, diuretic therapy and acute coronary syndrome should be supplemented in future research.

In conclusion, the MR analysis in this study unveiled a possible causal relationship between uric acid and heart failure. The findings suggest that elevated uric acid levels may heighten the risk of heart failure, providing a theoretical foundation for the prevention and treatment of this condition.

Funding

The work was supported by grants from the National Undergraduate Innovation and Entrepreneurship Training Program Project (202310164004).

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author statement

Jiaqi Zheng: Investigation, Data Curation, Methodology, Writing - Original draft, Formal analysis. Kaiwen Cen: Investigation, Data curation, Writing - Original draft preparation, Statistical analysis. Jiajun Zhang: Resources, Data collection. Huan Zhang: Supervision, Validation, Reviewing and Editing. Mingguang Zhao: Supervision, Validation, Reviewing and Editing. Xiaowen Hou: Conceptualization, Reviewing and Editing.

The first 2 authors contributed equally to this work.

Declaration of competing interest

None of the authors have conflicts of interest to declare.

Acknowledgments

We are really appreciative of all the participants in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.12.023.

References

[1] Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93(9):1137–46.
[2] Baman JR, Ahmad FS. Heart failure. JAMA 2020;324(10):1015.
[3] Bueno H, Moura B, Lancellotti P, Bauersachs J. The year in cardiovascular medicine 2020: heart failure and cardiomyopathies. Eur Heart J 2021;42(6):657–70.
[4] Wang Q, Wen X, Kong J. Recent progress on uric acid detection: a review. Crit Rev Anal Chem 2020;50(4):359–75.
[5] Ndrepepa G. Uric acid and cardiovascular disease. Clin Chim Acta 2018;484:150–63.
[6] Wu AH, Gladden JD, Ahmed M, Ahmed A, Filippatos G. Relation of serum uric acid to cardiovascular disease. Int J Cardiol 2016;213:4–7.
[7] Yu W, Cheng JD. Uric acid and cardiovascular disease: an update from molecular mechanism to clinical perspective. Front Pharmacol 2020;11:582680.
[8] Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: a review. Res Synth Methods 2019;10(4):486–96.
[9] Sekula P, Del Greco MF, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. J Am Soc Nephrol 2016;27(11):3253–65.
[10] Köttgen A, Albrecht E, Teumer A, et al. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. Nat Genet 2013;45(2):145–54.
[11] Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. Am J Epidemiol 2013;178(7):1177–84.
[12] Keenan T, Zhao W, Rasheed A, et al. Causal assessment of serum urate levels in cardiometabolic diseases through a mendelian randomization study. J Am Coll Cardiol 2016;67(4):407–16.
[13] Muiesan ML, Salvetti M, Virdis A, 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 2021;39(1):62–9.
[14] Stone ML, Richardson MR, Guevara L, Rand BG, Churilla JR. Elevated serum uric acid and self-reported heart failure in US adults: 2007-2016 national health and nutrition examination survey. Cardiorenal Med 2019;9(6):344–53.
[15] Huang H, Huang B, Li Y, et al. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail 2014;16(1):15–24.
[16] Kittleson MM, St John ME, Bead V, et al. Increased levels of uric acid predict haemodynamic compromise in patients with heart failure independently of B-type natriuretic peptide levels. Heart 2007;93(3):365–7.
[17] Cicero AF, Rosticci M, Parini A, Baronio C, D'Addato S, Borghi C. Serum uric acid is inversely proportional to estimated stroke volume and cardiac output in a large sample of pharmacologically untreated subjects: data from the Brisighella Heart Study. Intern Emerg Med 2014;9(6):655–60.
[18] Gherghina ME, Peride I, Tiglis M, Neagu TP, Niculae A, Checherita IA. Uric acid and oxidative stress-relationship with cardiovascular. Metabolic, and renal impairment. Int J Mol Sci 2022;23(6):3188.
[19] Casiglia E, Tikhonoff V, Virdis A, et al. Serum uric acid/serum creatinine ratio as a predictor of cardiovascular events. Detection of prognostic cardiovascular cut-off values. J Hypertens 2023;41(1):180–6.
[20] Maloberti A, Bombelli M, Facchetti R, et al. Relationships between diuretic-related hyperuricemia and cardiovascular events: data from the URic acid Right for heArt Health study. J Hypertens 2021;39(2):333–40.
[21] Rebora P, Centola M, Morici N, et al. Uric acid associated with acute heart failure presentation in acute coronary syndrome patients. Eur J Intern Med 2022;99:30–7.