Body mass index increases uric acid in East Asian population: a Mendelian randomization study

Mikyung Ryu
Kyonggi University
Sun Yeop Lee
Basgenbio, Co.
Sanghyuk Yoon
Basgenbio, Co.
Nayoung Kim
Basgenbio, Co.
Sol Lee
Basgenbio, Co.
Sun Ha Jee (jsunha@yuhs.ac)
Yonsei University

Research Article

Keywords: Body mass index, uric acid, Mendelian randomization, Korean Genome and Epidemiology Study, Biobank Japan, East Asia

Posted Date: July 7th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1790034/v1

Abstract

Background: Previous observational and Mendelian randomization studies suggested that the increase in serum uric acid causes adiposity, not vice versa. However, most findings came from data on European ancestry. Among East Asian populations, both directions in the causal relationship between adiposity and uric acid have been suggested by observational studies and a few MR studies. In this study, we tested the hypothesis of the causal effect of body mass index (BMI) on serum uric acid in East Asian populations.

Methods: Summary statistics from two large, publicly available biobanks from South Korea (72,299 participants in the Korean Genome and Epidemiology Study) and Japan (158,284 participants in the Biobank Japan) were utilized to conduct a two-sample Mendelian randomization study.

Results: We found that genetically determined BMI has a positive causal effect on serum uric acid in various Mendelian randomization methods (inverse-variance weighted: B [95% CI] = 0.029 [-0.006, 0.065]; simple mode: a [95% CI] = 0.053 [0.009, 0.097]); weighted mode: c [95% CI] = 0.036 [0.005, 0.067]); weighted median: k [95% CI] = 0.042 [0.019, 0.065]). Multiple robustness checks such as a funnel plot, leave-one-out analyses, and an MR-Egger regression did not suggest directional horizontal pleiotropy.

Conclusions: Genetically determined BMI increases serum uric acid in East Asian populations. Our findings from the South Korean and Japanese populations are consistent with previous observations in the European population.

1. Introduction

Uric acid, a normal component of urine, is a byproduct of the metabolic breakdown of purine nucleotides. Sustained elevation of uric acid in blood, or hyperuricemia, may occur due to excess production of uric acid due to increased levels of purine production or high cell turnover rate, and decreased excretion of uric acid due to metabolic acidosis or renal insufficiency (George & Minter, 2021). Hyperuricemia can lead to deposition of monosodium urate crystals in joints, tendons, and other tissues, which triggers recurrent episodes of pronounced acute inflammation, known as gout flares (Dalbeth et al., 2018; Kapetanovic et al., 2018).

The prevalence of hyperuricemia and gout has recently increased worldwide, especially in high-income countries such as United States and Ireland (Dehlin et al., 2020; L. Li et al., 2020) and East Asian countries such as China, South Korea, and Japan (Chen et al., 2017; Kim et al., 2018; Ogura et al., 2004). Incidence of gout has also been increasing in various geographic regions such as North America, Scandinavia, and South Korea (Dehlin et al., 2020).

As hyperuricemia and gout are often accompanied by a range of cardiovascular diseases and conditions, a number of observational studies and mendelian randomization (MR) studies has been conducted to investigate the direction of the causal relationships between serum uric acid level and adiposity-related or cardiometabolic measures or conditions such as body mass index (BMI) and coronary heart diseases (X.

Li et al., 2017). The MR studies collectively suggested that the effect estimates in the observational studies were confounded and that the uric acid does not cause adiposity and related health outcomes (Keenan et al., 2016; Lyngdoh et al., 2012; Oikonen et al., 2012; Rasheed et al., 2021; Sanderson et al., 2022; White et al., 2016). Instead, the causal effect of BMI on uric acid has been confirmed in multiple MR studies (Adams & Boutwell, 2021; Larsson et al., 2018; Lyngdoh et al., 2012; Oikonen et al., 2012; Palmer et al., 2013).

A MR study design is based on the assumption that allocation of alleles at a single locus occurs at random during gamete formation (Sanderson et al., 2022; Smith & Ebrahim, 2003). Under such an assumption, the distribution of a certain genetic variant is random respect to confounders of the relationship between an exposure and an outcome, and the genetic variant can be used as an instrumental variable (IV) in causal effect estimation. Compared to other observational study designs, results from a MR study may be at a lower risk of residual confounding and reverse causation, making it a powerful approach to assess a causal effect of complex exposure such as BMI. However, most of the previous MR studies for the relationship between BMI and uric acid were based on data sources of European ancestry. Among East Asian populations, both directions (i.e., uric acid to adiposity or adiposity to uric acid) in the causal relationship between adiposity and uric acid have been suggested by observational studies (Kuwabara et al., 2018; D. mei Liu et al., 2019; Y. R. Liu et al., 2021; Sakata et al., 2020; Seki et al., 2020; Tanaka et al., 2015) and a few MR studies (Feng et al., 2022; Hong et al., 2020; Jiang et al., 2020; L. Wang et al., 2020).

Therefore, in this study, a two-sample MR study was conducted to test the hypothesis of the causal effect of BMI on uric acid in East Asian populations. Summary statistics from two large, publicly available biobanks from South Korea and Japan were utilized.

2. Methods

2.1. Summary data

The biobanks from two East Asian samples, South Koreans and Japanese, were chosen as they do not overlap and should share similarities in patterns of linkage disequilibrium, meaning that the associations of the genetic variants with the exposure of interest or other variables on pleiotropic pathways are similar in the two samples.

The genome-wide association study (GWAS) summary statistics from the Korean Genome Epidemiology Study (KoGES) were utilized for the associations between genetic variants and BMI, which were only utilized in our two-sample MR study. The KoGES is a consortium project that includes multiple population-wide prospective cohorts in South Korea (Kim et al., 2017). Since 2003, the KoGES has collected epidemiologic, clinical, and genomic information from a total of 225,396 individuals. The genotype data used in this study were from three separate cohorts within the KoGES: the Ansan and

Ansung study, the health examinee study, and the cardiovascular disease association study. Details of the KoGES are described elsewhere (Kim et al., 2017).

The GWAS summary statistics from the Biobank Japan (BBJ) were utilized for the association between genetic variants and BMI, and for the association between genetic variants and uric acid. The BBJ is a publicly available biobank of 199,982 Japanese participants (Nagai et al., 2017). Initiated in 2003, the BBJ constructed a large-scale, multi-institutional, hospital-based biobank. Through interviews and medical record reviews, it collected DNA, serum, and clinical information from patients with any of 47 target diseases between 2003 and 2007 from 66 hospitals affiliated with 12 medical institutes in Japan. Details of the BBJ are described elsewhere (Nagai et al., 2017).

2.2. Genetic variants as instrumental variables

Genotyping procedures for the KoGES (Han et al., 2021) and the BBJ (Nakatochi et al., 2019) are described in detail elsewhere. Briefly, in the KoGES, 72,299 participants were genotyped using Affymetrix or Illumina platforms. For the genotyping quality control procedures, samples with low call rate (< 0.90) and single nucleotide polymorphisms (SNPs) with low call rate (< 0.95), low minor allele frequency (< 0.01), or failure to verify Hardy-Weinberg equilibrium ($p < 1.0 \times 10^{-6}$) were excluded. Variants were imputed using the Korean Reference Genome initiated by Center of Genome Science (CGS) of Korea National Institute of Health and the East Asian data from the 1000 Genomes Project Phase 3 (NCBI build 37) as the reference. The imputation process included quality checks for metrics such as strand flips, allele flips, and missingness. Imputation was conducted using either ShapeIT v2 (Delaneau et al., 2012) or IMPUTE v2 (Marchini et al., 2007). Only SNPs with information content metric score larger than 0.6 were included.

For the BBJ, samples were genotyped on Illumina platforms. Samples with low call rates (< 0.98), non-East Asian samples, or closely related samples identified by identity by state and SNPs with low call rate (< 0.99), low minor allele frequency (< 0.01), or failure to verify Hardy-Weinberg equilibrium ($p < 1.0 \times 10^{-6}$) were excluded. Variants were imputed with Minimac and the 1000 Genomes Project Phase 1 (version 3) East Asian reference haplotypes.

Based on data-driven approaches, 26 genetic variants were selected for IVs in the KoGES for their associations with BMI. For a multifactorial exposure such as BMI, such a polygenic approach is more feasible rather than a biologically-driven approach, where a single variant, often a *cis* variant, is selected (Holmes et al., 2021). The data-driven approaches to variant selection are as follows. First, only SNPs at the genome-wide significance level ($p < 5 \times 10^{-8}$) were chosen. The threshold is commonly used in GWAS to reduce type 1 error inflated by multiple testing (Belmont et al., 2005; Pe'er et al., 2008). Second, SNPs with the F statistic larger than 10, a conventional threshold for adequate strength for IVs, were included. Third, using a clumping procedure in PLINK v1.9 (http://www.cog-genomics.org/plink/1.9/), SNPs were combined at a pre-defined threshold of linkage disequilibrium ($r^2 < 0.001$ in a 10-Mb window).

2.3. Ascertainment of body mass index and serum uric acid

At each baseline survey of the KoGES, body weight and height were measured to the nearest tenth kilogram and centimeter. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Information on serum uric acid in the BBJ was retrieved from medical records of routine laboratory examination for 109,209 patients aged between 18 and 85 years (Nakatochi et al., 2019). Patients with urate-lowering therapy (i.e., allopurinol, febuxostat, probenecid, or benzbromarone) or renal insufficiency (< 15 ml min^{-1} 1.73 m^{-2}) were excluded. Serum uric acid was adjusted for age, biological sex, top ten principal components of genetic ancestry, and target disease status (present vs. absent) in a linear regression. Resulting residuals were standardized a rank-based inverse-normal transformation (Kanai et al., 2018).

2.4. Statistical analyses

An MR analytic approach is an IV method which uses genetic variants, or SNPs, as IVs for an independent variable of interest, assuming genotypes are assigned randomly at conception, and mating is not associated with genotype (Sanderson et al., 2022; Smith & Ebrahim, 2003). Paralleling a randomized controlled trial, an MR study design enables causal hypothesis testing by addressing potential confounding in observational data when the following three assumptions are met: 1) SNPs are associated with an exposure (e.g., BMI) (i.e., relevance assumption), 2) SNPs affect an outcome (e.g., uric acid) only through their effect on the exposure (i.e., exclusion restriction assumption), and 3) there are no confounders for the association between SNPs and the outcome (i.e., independence assumption).

The fixed-effect inverse variance weighted (IVW) method, in which the gene-outcome association is regressed on the gene-exposure association, was used as a primary MR analysis (Burgess et al., 2013). The IVW method is valid and statistically efficient under the assumption that all SNPs included are valid IVs. Several sensitivity analyses were also performed. First, a Cochran's Q statistic was calculated to investigate the presence of between-SNP heterogeneity in the causal effect estimates (Greco M et al., 2015). Second, a funnel plot was produced to visually compare the potential directional horizontal pleiotropy for the selected SNPs (Burgess et al., 2017; Sterne et al., 2011). Third, SNPs were excluded one by one, and the IVW was performed on the remaining SNPs to identify the potential impact of outlying SNPs on the effect estimate (i.e., leave-one-out analyses) (Burgess et al., 2020). Fourth, a simple mode method and a weighted mode method were performed, in which the most frequent value among effect estimates is without horizontal pleiotropy (Hartwig et al., 2017). Fifth, a weighted median method was performed, which provides consistent estimates when at least 50% of the SNPs are valid IVs (Rasheed et al., 2014). Sixth, the MR-Egger regression was performed to assess a potential violation of the exclusion restriction assumption due to horizontal pleiotropy (Bowden et al., 2015). Under the Instrument Strength Independent of Direct Effect assumption, the MR-Egger regression intercept that differs from zero ($p < 0.05$) indicates the presence of horizontal pleiotropy, and the slope is a pleiotropy-adjusted causal effect estimate of the exposure of interest. Details of the present study are reported according to a reporting

guideline for a Mendelian randomization study, STROBE-MR (Skrivankova et al., 2021). All data analyses were performed in R 4.0.3 (R Core Team, 2020).

3. Results

For the 26 genetic variants selected as IVs, between-SNP heterogeneity in the causal effect of genetically determined BMI on uric acid was substantial (Cochran's Q = 157.500) (Table 1), suggesting potential horizontal pleiotropy. In addition, a forest plot (Fig. 1a) and a funnel plot (Supplementary Fig. 1) of the SNP-specific effect estimates suggested the presence of outlying SNPs. However, the funnel plot did not show a systematic pattern of directional pleiotropy. Also, leave-one-out analyses confirmed that that the pooled causal effect estimate from the SNPs was not driven by any single SNP (Fig. 1b).

Table 1
Mendelian randomization estimates for the causal effect of body mass index on serum uric acid

	Estimate [95% CI]	**p-value**
Test for heterogeneity (Cochran's Q)	157.500	< 0.001
Test for directional horizontal pleiotropy (MR-Egger intercept)	0.004 [-0.010, 0.018]	0.573
Causal effect estimates		
Inverse-variance weighted	0.029 [-0.006, 0.065]	0.105
Simple mode	0.053 [0.009, 0.097]	0.027
Weighted mode	0.036 [0.005, 0.067]	0.032
Weighted median	0.042 [0.019, 0.065]	< 0.001
MR-Egger	-0.002 [-0.113, 0.110]	0.979
MR, Mendelian randomization; CI, confidence interval.		

The positive causal effect of genetically determined BMI on serum uric acid was observed in various MR methods (IVW: β [95% CI] = 0.029 [-0.006, 0.065]; simple mode: β [95% CI] = 0.053 [0.009, 0.097]); weighted mode: β [95% CI] = 0.036 [0.005, 0.067]); weighted median: β [95% CI] = 0.042 [0.019, 0.065]) (Table 1; Fig. 2). While the causal effect estimate from the MR-Egger regression was not statistically significant (β [95% CI] = -0.002 [-0.113, 0.110]), there was also no evidence of directional horizontal pleiotropy from the MR-Egger regression intercept (β [95% CI] = 0.004 [-0.010, 0.018]).

4. Discussion

In the two-sample MR study using data from samples from two East Asian countries, South Korea and Japan, we tested whether BMI had a causal effect on serum uric acid. Using several MR analytic

methods, we found that genetically determined BMI was positively associated with serum uric acid in the East Asian populations, which is consistent with previous findings in populations of European ancestry.

While findings from observational studies consistently suggested the robust relationship between BMI or other adiposity-related health outcomes and uric acid, the direction of the causal pathway could not be easily inferred from the observational data due to issues of potential residual confounding and reverse causation. For causal hypothesis testing, the MR design has been recently utilized in multiple studies, and they concluded that adiposity or BMI affects uric acid, rather than the other direction. In particular, there was no evidence that uric acid has a causal effect on BMI (Lyngdoh et al., 2012; Oikonen et al., 2012), weight (Lyngdoh et al., 2012), fat mass (Lyngdoh et al., 2012), and waist circumference (Lyngdoh et al., 2012), and also on adiposity-related health outcomes such as intima-media thickness (Oikonen et al., 2012), triglycerides (Rasheed et al., 2014), and coronary heart diseases (Efstathiadou et al., 2019; Palmer et al., 2013; White et al., 2016). Conversely, the positive causal effect of BMI on uric acid has been consistently reported in a number of MR studies (Adams & Boutwell, 2021; Larsson et al., 2018; Lyngdoh et al., 2012; Oikonen et al., 2012; Palmer et al., 2013). The findings of the causal effect of BMI have also been extended to gout incidence, one of the sequelae of increased uric acid (i.e., hyperuricemia) (Evans et al., 2018; Larsson et al., 2018). Moreover, weight loss by bariatric surgery was also found to decrease the level of uric acid and reduce the risk of gout (Yeo et al., 2019).

However, the same relationship had not been well-established in East Asian populations. The suggestive evidence from observational findings exists for both directions of potential causal pathways between adiposity or related health conditions and uric acid. For example, in the Japanese population, the associations between uric acid and subsequent hypertension (Kuwabara et al., 2018), metabolic syndrome (Seki et al., 2020), and cardiovascular mortality (Sakata et al., 2020) have been reported using observational data. One MR study with the South Korean population found the causal effect of uric acid on atrial fibrillation in men, but not in women (Hong et al., 2020), while two other MR studies with the Chinese population did not find a causal effect of uric acid on arterial stiffness (Jiang et al., 2020) or metabolic syndrome (L. Wang et al., 2020). For the causal direction from adiposity to uric acid in the East Asian population, there are also a number of observational findings for the effect of BMI, body adiposity index, lipid accumulation product, and cardiometabolic index (Dong et al., 2017; He et al., 2022; D. mei Liu et al., 2019; Y. R. Liu et al., 2021; H. Wang et al., 2018), including one from a Japanese twin study (Tanaka et al., 2015). One MR study with the Japanese and Chinese populations also found the causal effect of BMI on uric acid (Feng et al., 2022).

Our finding from the East Asian populations is consistent with the causal effect of BMI on uric acid previously found in the European population, adding support for the causal relationship being universal across different populations. As the prevalence of overweight and obesity has been increasing in the East Asian populations (Bentham et al., 2017), the increase in body mass index and adiposity may be a culprit of the recent increase in the prevalence of hyperuricemia and gout in these populations (Chen et al., 2017; Dehlin et al., 2020; Kim et al., 2018; Ogura et al., 2004). Moreover, the contribution of high body mass index on mortality and diseases has also been exacerbating (Stanaway et al., 2018).

As with any MR study, our studies have several limitations. First, weak instrument bias may be at play, but in a two-sample MR setting, the bias pushes the magnitude of causal effect estimates towards the null, reducing the likelihood of false positive findings (Burgess et al., 2020). Second, despite multiple robustness checks for directional horizontal pleiotropy, such as the MR-Egger regressions and the leave-one-out analyses, the exclusion restriction assumption cannot be guaranteed. Third, while we attempted to control for population stratification by including only East Asian samples, the assumption of no confounding cannot be guaranteed and may be violated by dynastic effects or assortative mating. Fourth, utilization of the published summary statistics did not allow subgroup analyses or modification to covariate adjustment when generating the summary statistics. Fifth, BMI was only measured at one point in time. Its time-varying effect could not be investigated.

5. Conclusion

In the South Korean and the Japanese populations, we found that BMI had a positive causal effect on serum uric acid, which is a consistent pattern previously observed in individuals with European ancestry. Future studies should investigate whether the mediators of the causal relationship, and whether the relationship varies by biological sex or over the lifecourse, which would improve our understanding of the mechanism and potentially shed light on how to intervene.

Abbreviations

BBJ: the Biobank Japan

BMI: body mass index

CI: confidence intervals

GWAS: genome-wide association study

IV: instrumental variable

IVW: inverse-variance weighted

KoGES: the Korean Genome and Epidemiology Study

MR: Mendelian randomization

SE: standard error

SNP: single nucleotide polymorphism

STROBE: Strengthening the reporting of observational studies in epidemiology

Declarations

Ethics approval and consent to participate

All participants gave informed consent to participate in the KoGES and the BBJ.

Consent for publication

Not applicable.

Availability of data and materials

Data for this study are available on application to KoGES (nih.go.kr/eng/) and Biobank Japan (biobankjp.org/en/).

Competing interests

None.

Funding

None.

Authors' contributions

MR and SHJ conceptualized and designed the study. SHJ performed the data analysis. SYL drafted the manuscript. All authors interpreted the findings, provided revisions, and approved the final version of the manuscript for publication.

Acknowledgement

None.

References

1. Adams, C. D., & Boutwell, B. B. (2021). Using multiple Mendelian randomization approaches and genetic correlations to understand obesity, urate, and gout. Scientific Reports, *11*(1), 1–11.
2. Belmont, J. W., Boudreau, A., Leal, S. M., Hardenbol, P., Pasternak, S., Wheeler, D. A., Willis, T. D., Yu, F., Yang, H., Gao, Y., Hu, H., Hu, W., Li, C., Lin, W., Liu, S., Pan, H., Tang, X., Wang, J., Wang, W., … Stewart, J. (2005). A haplotype map of the human genome. Nature 2005 *437:7063*, *437*(7063), 1299–1320.
3. Bentham, J., di Cesare, M., Bilano, V., Bixby, H., Zhou, B., Stevens, G. A., Riley, L. M., Taddei, C., Hajifathalian, K., Lu, Y., Savin, S., Cowan, M. J., Paciorek, C. J., Chirita-Emandi, A., Hayes, A. J., Katz, J., Kelishadi, R., Kengne, A. P., Khang, Y. H., … Cisneros, J. Z. (2017). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. The Lancet, *390*(10113), 2627–2642.

4. Bowden, J., Smith, G. D., & Burgess, S. (2015). Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. International Journal of Epidemiology, *44*(2), 512.
5. Burgess, S., Bowden, J., Fall, T., Ingelsson, E., & Thompson, S. G. (2017). Sensitivity analyses for robust causal inference from mendelian randomization analyses with multiple genetic variants. Epidemiology, *28*(1), 30–42.
6. Burgess, S., Butterworth, A., & Thompson, S. G. (2013). Mendelian randomization analysis with multiple genetic variants using summarized data. Genetic Epidemiology, *37*(7), 658–665.
7. Burgess, S., Davey Smith, G., Davies, N. M., Dudbridge, F., Gill, D., Glymour, M. M., Hartwig, F. P., Holmes, M. V., Minelli, C., Relton, C. L., & Theodoratou, E. (2020). Guidelines for performing Mendelian randomization investigations. Wellcome Open Research, *4*.
8. Chen, Y., Tang, Z., Huang, Z., Zhou, W., Li, Z., Li, X., & Sun, F. (2017). The prevalence of gout in mainland China from 2000 to 2016: a systematic review and meta-analysis. Journal of Public Health 2017 *25:5*, *25*(5), 521–529.
9. Dalbeth, N., Phipps-Green, A., Frampton, C., Neogi, T., Taylor, W. J., & Merriman, T. R. (2018). Relationship between serum urate concentration and clinically evident incident gout: an individual participant data analysis. Annals of the Rheumatic Diseases, *77*(7), 1048–1052.
10. Dehlin, M., Jacobsson, L., & Roddy, E. (2020). Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. In *Nature Reviews Rheumatology* (Vol. 16, Issue 7, pp. 380–390). Nature Publishing Group.
11. Delaneau, O., Marchini, J., & Zagury, J. F. (2012). A linear complexity phasing method for thousands of genomes. Nature Methods, *9*(2), 179–181. https://doi.org/10.1038/nmeth.1785
12. Dong, H., Xu, Y., Zhang, X., & Tian, S. (2017). Visceral adiposity index is strongly associated with hyperuricemia independently of metabolic health and obesity phenotypes. Scientific Reports *2017 7:1*, *7*(1), 1–13.
13. Efstathiadou, A., Gill, D., McGrane, F., Quinn, T., & Dawson, J. (2019). Genetically determined uric acid and the risk of cardiovascular and neurovascular diseases: A mendelian randomization study of outcomes investigated in randomized trials. Journal of the American Heart Association, *8*(17).
14. Evans, P. L., Prior, J. A., Belcher, J., Mallen, C. D., Hay, C. A., & Roddy, E. (2018). Obesity, hypertension and diuretic use as risk factors for incident gout: a systematic review and meta-analysis of cohort studies. Arthritis Research & Therapy, *20*(1).
15. Feng, Y., Fu, M., Guan, X., Wang, C., Yuan, F., Bai, Y., Meng, H., Li, G., Wei, W., Li, H., Li, M., Jie, J., Lu, Y., & Guo, H. (2022). Uric Acid Mediated the Association Between BMI and Postmenopausal Breast Cancer Incidence: A Bidirectional Mendelian Randomization Analysis and Prospective Cohort Study. *Frontiers in Endocrinology*, *12*, 1928.
16. George, C., & Minter, D. A. (2021). Hyperuricemia. Urology at a Glance, 107–109.
17. Greco M, F. del, Minelli, C., Sheehan, N. A., & Thompson, J. R. (2015). Detecting pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. Statistics in

Medicine, *34*(21), 2926–2940.

18. Han, N., Oh, J. M., & Kim, I. W. (2021). Combination of genome-wide polymorphisms and copy number variations of pharmacogenes in Koreans. Journal of Personalized Medicine, *11*(1), 1–11.
19. Hartwig, F. P., Smith, G. D., & Bowden, J. (2017). Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. International Journal of Epidemiology, *46*(6), 1985–1998.
20. He, H., Pan, L., Ren, X., Wang, D., Du, J., Cui, Z., Zhao, J., Wang, H., Wang, X., Liu, F., Pa, L., Peng, X., Wang, Y., Yu, C., & Shan, G. (2022). The Effect of Body Weight and Alcohol Consumption on Hyperuricemia and Their Population Attributable Fractions: A National Health Survey in China. Obesity Facts, *15*(2), 216–227.
21. Holmes, M. V., Richardson, T. G., Ference, B. A., Davies, N. M., & Davey Smith, G. (2021). Integrating genomics with biomarkers and therapeutic targets to invigorate cardiovascular drug development. Nature Reviews Cardiology, *18*(6), 435–453.
22. Hong, M., Park, J. W., Yang, P. S., Hwang, I., Kim, T. H., Yu, H. T., Uhm, J. S., Joung, B., Lee, M. H., Jee, S. H., & Pak, H. N. (2020). A mendelian randomization analysis: The causal association between serum uric acid and atrial fibrillation. European Journal of Clinical Investigation, *50*(10), e13300.
23. Jiang, Y., Ge, J. Y., Zhang, Y. Y., Wang, F. F., Ji, Y., & Li, H. Y. (2020). The relationship between elevated serum uric acid and arterial stiffness in a healthy population. Vascular, *28*(4), 494–501.
24. Kanai, M., Akiyama, M., Takahashi, A., Matoba, N., Momozawa, Y., Ikeda, M., Iwata, N., Ikegawa, S., Hirata, M., Matsuda, K., Kubo, M., Okada, Y., & Kamatani, Y. (2018). Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. Nature Genetics 2018 *50:3*, *50*(3), 390–400.
25. Kapetanovic, M. C., Nilsson, P., Turesson, C., Englund, M., Dalbeth, N., & Jacobsson, L. (2018). The risk of clinically diagnosed gout by serum urate levels: Results from 30 years follow-up of the Malmö preventive project cohort in southern Sweden. Arthritis Research and Therapy, *20*(1), 1–10.
26. Keenan, T., Zhao, W., Rasheed, A., Ho, W. K., Malik, R., Felix, J. F., Young, R., Shah, N., Samuel, M., Sheikh, N., Mucksavage, M. L., Shah, O., Li, J., Morley, M., Laser, A., Mallick, N. H., Zaman, K. S., Ishaq, M., Rasheed, S. Z., … Saleheen, D. (2016). Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study. Journal of the American College of Cardiology, *67*(4), 407–416.
27. Kim, Y., Han, B. G., Moon, H. K., Song, J. H., & Yun, Y. min. (2017). Cohort Profile: The Korean Genome and Epidemiology Study (KoGES) Consortium. *International Journal of Epidemiology*, *46*(2), e20–e20.
28. Kim, Y., Kang, J., & Kim, G. T. (2018). Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clinical Rheumatology 2018 *37:9*, *37*(9), 2529–2538.
29. Kuwabara, M., Hisatome, I., Niwa, K., Hara, S., Roncal-Jimenez, C. A., Bjornstad, P., Nakagawa, T., Andres-Hernando, A., Sato, Y., Jensen, T., Garcia, G., Rodriguez-Iturbe, B., Ohno, M., Lanaspa, M. A., &

Johnson, R. J. (2018). Uric Acid Is a Strong Risk Marker for Developing Hypertension from Prehypertension:A 5-Year Japanese Cohort Study. Hypertension, *71*(1), 78–86.

30. Larsson, S. C., Burgess, S., & Michaëlsson, K. (2018). Genetic association between adiposity and gout: A Mendelian randomization study. Rheumatology (United Kingdom), *57*(12), 2145–2148.
31. Li, L., Zhang, Y., & Zeng, C. (2020). Update on the epidemiology, genetics, and therapeutic options of hyperuricemia. In *American Journal of Translational Research* (Vol. 12, Issue 7, pp. 3167–3181). e-Century Publishing Corporation.
32. Li, X., Meng, X., Timofeeva, M., Tzoulaki, I., Tsilidis, K. K., Ioannidis, P. A., Campbell, H., & Theodoratou, E. (2017). Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. *BMJ*, *357*.
33. Liu, D. mei, Jiang, L. di, Gan, L., Su, Y., & Li, F. (2019). Association between serum uric acid level and body mass index in sex- And age-specific groups in southwestern China. Endocrine Practice, *25*(5), 438–445.
34. Liu, Y. R., Tantoh, D. M., Lin, C. C., Hsiao, C. H., & Liaw, Y. P. (2021). Risk of gout among Taiwanese adults with ALDH-2 rs671 polymorphism according to BMI and alcohol intake. Arthritis Research and Therapy, *23*(1), 1–12.
35. Lyngdoh, T., Vuistiner, P., Marques-Vidal, P., Rousson, V., Waeber, G., Vollenweider, P., & Bochud, M. (2012). Serum uric acid and adiposity: Deciphering causality using a bidirectional mendelian randomization approach. PLoS ONE, *7*(6), e39321.
36. Marchini, J., Howie, B., Myers, S., McVean, G., & Donnelly, P. (2007). A new multipoint method for genome-wide association studies by imputation of genotypes. Nature Genetics, *39*(7), 906–913.
37. Nagai, A., Hirata, M., Kamatani, Y., Muto, K., Matsuda, K., Kiyohara, Y., Ninomiya, T., Tamakoshi, A., Yamagata, Z., Mushiroda, T., Murakami, Y., Yuji, K., Furukawa, Y., Zembutsu, H., Tanaka, T., Ohnishi, Y., Nakamura, Y., Cooperative, J., Group, H., & Kubo, M. (2017). *Overview of the BioBank Japan Project: Study design and profile*.
38. Nakatochi, M., Kanai, M., Nakayama, A., Hishida, A., Kawamura, Y., Ichihara, S., Akiyama, M., Ikezaki, H., Furusyo, N., Shimizu, S., Yamamoto, K., Hirata, M., Okada, R., Kawai, S., Kawaguchi, M., Nishida, Y., Shimanoe, C., Ibusuki, R., Takezaki, T., … Matsuo, H. (2019). Genome-wide meta-analysis identifies multiple novel loci associated with serum uric acid levels in Japanese individuals. Communications Biology 2019 *2:1*, *2*(1), 1–10.
39. Ogura, T., Matsuura, K., Matsumoto, Y., Mimura, Y., Kishida, M., Otsuka, F., & Tobe, K. (2004). Recent trends of hyperuricemia and obesity in Japanese male adolescents, 1991 through 2002. Metabolism: Clinical and Experimental, *53*(4), 448–453.
40. Oikonen, M., Wendelin-Saarenhovi, M., Lyytikäinen, L. P., Siitonen, N., Loo, B. M., Jula, A., Seppälä, I., Saarikoski, L., Lehtimäki, T., Hutri-Kähönen, N., Juonala, M., Kähönen, M., Huupponen, R., Viikari, J. S. A., & Raitakari, O. T. (2012). Associations between serum uric acid and markers of subclinical atherosclerosis in young adults. The cardiovascular risk in Young Finns study. Atherosclerosis, *223*(2), 497–503. https://doi.org/10.1016/j.atherosclerosis.2012.05.036

41. Palmer, T. M., Nordestgaard, B. G., Benn, M., Tybjarg-Hansen, A., Smith, G. D., Lawlor, D. A., & Timpson, N. J. (2013). Association of plasma uric acid with ischaemic heart disease and blood pressure: Mendelian randomization analysis of two large cohorts. *BMJ (Online)*, *347*(7919).
42. Pe'er, I., Yelensky, R., Altshuler, D., & Daly, M. J. (2008). Estimation of the multiple testing burden for genomewide association studies of nearly all common variants. Genetic Epidemiology, *32*(4), 381–385.
43. R Core Team. (2020). *R: A language and environment for statistical computing.* (4.0.3). R Foundation for Statistical Computing.
44. Rasheed, H., Hughes, K., Flynn, T. J., & Merriman, T. R. (2014). Mendelian randomization provides no evidence for a causal role of serum urate in increasing serum triglyceride levels. Circulation: Cardiovascular Genetics, *7*(6), 830–837.
45. Rasheed, H., Zheng, J., Rees, J., Sanderson, E., Thomas, L., Richardson, T. G., Fang, S., Bekkevold, O. J., Stovner, E. B., Gabrielsen, M. E., Skogholt, A. H., Romundstad, S., Brumpton, B., Hallan, S., Willer, C., Burgess, S., Hveem, K., Smith, G. D., Gaunt, T. R., & Åsvold, B. O. (2021). The causal effects of serum lipids and apolipoproteins on kidney function: multivariable and bidirectional Mendelian-randomization analyses. International Journal of Epidemiology, *50*(5), 1569–1579.
46. Sakata, S., Hata, J., Honda, T., Hirakawa, Y., Oishi, E., Shibata, M., Yoshida, D., Goto, K., Kitazono, T., & Ninomiya, T. (2020). Serum uric acid levels and cardiovascular mortality in a general Japanese population: the Hisayama Study. Hypertension Research, *43*(6), 560–568.
47. Sanderson, E., Glymour, M. M., Holmes, M. v., Kang, H., Morrison, J., Munafò, M. R., Palmer, T., Schooling, C. M., Wallace, C., Zhao, Q., & Davey Smith, G. (2022). Mendelian randomization. Nature Reviews Methods Primers, *2*(1), 1–21.
48. Seki, R., Kimura, T., Inoue, K., & Seki, R. (2020). Serum Uric Acid Level Has Stronger Correlations with Metabolic Syndrome-Related Markers in Women than in Men in a Japanese Health Check-Up Population. Open Journal of Epidemiology, *10*(04), 399–418.
49. Skrivankova, V. W., Richmond, R. C., Woolf, B. A. R., Yarmolinsky, J., Davies, N. M., Swanson, S. A., Vanderweele, T. J., Higgins, J. P. T., Timpson, N. J., Dimou, N., Langenberg, C., Golub, R. M., Loder, E. W., Gallo, V., Tybjaerg-Hansen, A., Davey Smith, G., Egger, M., & Richards, J. B. (2021). Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. JAMA, *326*(16), 1614–1621.
50. Smith, G. D., & Ebrahim, S. (2003). "Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? Great Britain International Journal of Epidemiology, *32*, 1–22.
51. Stanaway, J. D., Afshin, A., Gakidou, E., Lim, S. S., Abate, D., Abate, K. H., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, M., Abebe, Z., Abera, S. F., Abil, O. Z., Abraha, H. N., … Murray, C. J. L. (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and

metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. The Lancet, *392*(10159), 1923–1994.

52. Sterne, J. A. C., Sutton, A. J., Ioannidis, J. P. A., Terrin, N., Jones, D. R., Lau, J., Carpenter, J., Rücker, G., Harbord, R. M., Schmid, C. H., Tetzlaff, J., Deeks, J. J., Peters, J., Macaskill, P., Schwarzer, G., Duval, S., Altman, D. G., Moher, D., & Higgins, J. P. T. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*, *343*(7818).
53. Tanaka, K., Ogata, S., Tanaka, H., Omura, K., Honda, C., & Hayakawa, K. (2015). The relationship between body mass index and uric acid: a study on Japanese adult twins. Environmental Health and Preventive Medicine, *20*(5), 347–353.
54. Wang, H., Sun, Y., Wang, S., Qian, H., Jia, P., Chen, Y., Li, Z., & Zhang, L. (2018). Body adiposity index, lipid accumulation product, and cardiometabolic index reveal the contribution of adiposity phenotypes in the risk of hyperuricemia among Chinese rural population. Clinical Rheumatology, *37*(8), 2221–2231.
55. Wang, L., Zhang, T., Liu, Y., Tang, F., & Xue, F. (2020). Association of Serum Uric Acid with Metabolic Syndrome and Its Components: A Mendelian Randomization Analysis. *BioMed Research International*, *2020*.
56. White, J., Sofat, R., Hemani, G., Shah, T., Engmann, J., Dale, C., Shah, S., Kruger, F. A., Giambartolomei, C., Swerdlow, D. I., Palmer, T., McLachlan, S., Langenberg, C., Zabaneh, D., Lovering, R., Cavadino, A., Jefferis, B., Finan, C., Wong, A., … Hingorani, A. D. (2016). Plasma urate concentration and risk of coronary heart disease: a Mendelian randomisation analysis. The Lancet Diabetes & Endocrinology, *4*(4), 327–336.
57. Yeo, C., Kaushal, S., Lim, B., Syn, N., Oo, A. M., Rao, J., Koura, A., & Yeo, D. (2019). Impact of bariatric surgery on serum uric acid levels and the incidence of gout—A meta-analysis. Obesity Reviews, *20*(12), 1759–1770.

Figures

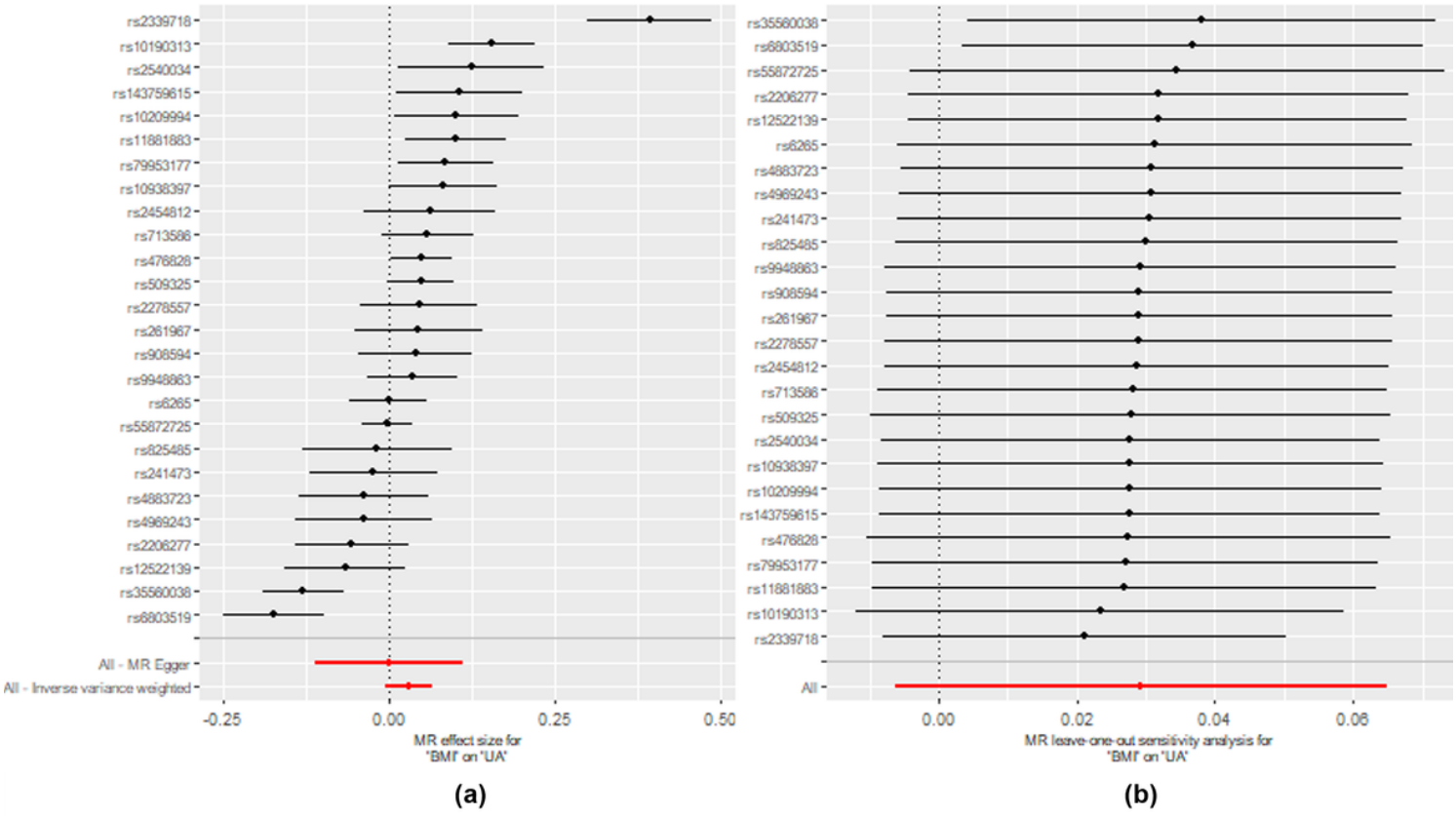

Figure 1

Forest plots of SNP-specific Mendelian randomization effect estimates (a) and leave-one-out analyses (b).

MR, Mendelian randomization; BMI, body mass index; UA, uric acid; SNP, single nucleotide polymorphism.

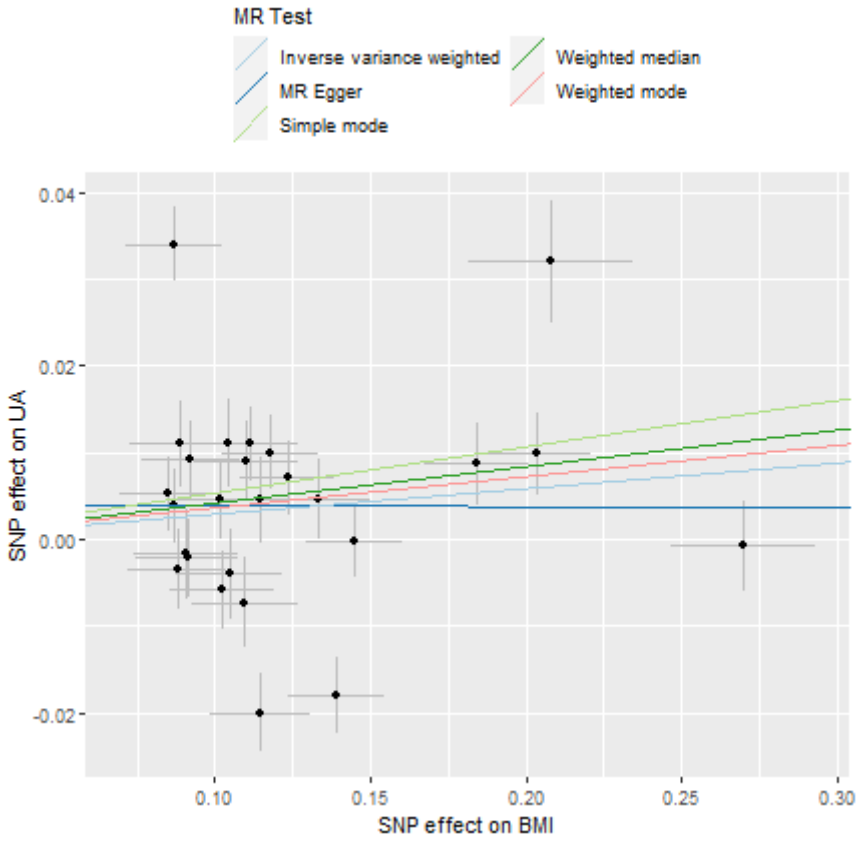

Figure 2

A scatter plot of SNP-BMI associations (x-axis) against SNP-uric acid associations (y-axis). Each data point indicates a SNP-specific estimate and the gray lines crossing the dots indicate 95% confidence intervals. Slopes of the colored lines indicate the Mendelian randomization effect estimates for each method.

MR, Mendelian randomization; SNP, single nucleotide polymorphism; UA, uric acid; BMI, body mass index.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.png