Coffee Consumption Reduces Gout Risk Independently of Serum Uric Acid Levels: Mendelian Randomization Analyses Across Ancestry Populations

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**Objective.** The effects of coffee consumption on serum uric acid (SUA) levels and gout risk are controversial. There have hitherto been no reports based on Mendelian randomization (MR) analysis of its effects that consider pleiotropy. Here, we evaluated the effects of coffee consumption across ancestry populations, taking pleiotropy into account.

**Methods.** We performed the first MR analyses for coffee consumption on SUA levels and gout, considering pleiotropy. We used the following summary statistics of genome-wide association studies from a Japanese population: habitual coffee consumption (152,634 subjects), gout (3053 cases and 4554 controls), and SUA levels (121,745 subjects). In addition to fixed-effect inverse variance weighted (IVW) meta-analysis, we performed a robust evaluation of heterogeneity and removed several instruments for reasons of possible pleiotropy. Previous European datasets were also reevaluated while heterogeneity was considered.

**Results.** Habitual coffee consumption was significantly and inversely associated with gout (odds ratio [OR] = 0.29, 95% confidence interval [95% CI]: 0.16-0.51, \(P = 1.9 \times 10^{-5}\)) in random-effect IVW (\(P_{\text{het}} = 5.5 \times 10^{-19}\)). Excluding pleiotropic instruments, the protective effect on gout was confirmed in fixed-effect IVW analysis (OR = 0.75, 95% CI: 0.58-0.97, \(P = 0.026\)) without heterogeneity (\(P_{\text{het}} = 0.39\)). However, we observed no significance in the previous European datasets when heterogeneity was considered. Associations were not observed between coffee consumption and SUA levels in either ancestry in MR analyses that considered pleiotropy. Multivariable MR analysis showed that increased coffee consumption significantly reduced gout risk, even after adjusting for SUA levels (OR = 0.50, 95% CI: 0.31-0.81, \(P = 0.0046\)).

**Conclusion.** With pleiotropy taken into account, our MR analyses revealed that coffee consumption can causally reduce gout risk, and that it may reduce gout risk independently of SUA levels.

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Members of the Japan Gout Genomics Consortium are shown in Appendix A.

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INTRODUCTION

Gout is a common arthritis that results from hyperuricemia due to environmental and genetic factors. Previous observational studies have shown an inverse association between habitual coffee consumption and gout (1). In 2018, Larsson et al performed a Mendelian randomization (MR) analysis using genome-wide association study (GWAS) data in Europeans to infer the causal effects of coffee consumption on gout, which showed that coffee consumption can reduce gout risk (2). However, as Lee pointed out in his corresponding letter (3) to the report by Larsson et al (2), pleiotropy should be considered in MR analyses, and other approaches, including the random effect inverse variance weighted (IVW) meta-analysis, should be applied to adjust the causal effect and achieve a robust assessment. Hitherto there have been no reports on MR analysis that investigate the association between coffee consumption and gout susceptibility while taking pleiotropy into account. MR is also generally performed within a single ancestry, whereas validations within independent ancestries are necessary.

Here, to clarify the question of whether or not habitual coffee consumption is causally associated with serum uric acid (SUA) levels and gout risk, we performed the first MR analysis of the effect of coffee consumption on SUA levels and gout considering pleiotropy.

Furthermore, we reanalyzed the European datasets reported by Larsson et al (2), taking the heterogeneity into account. Considering the heterogeneity of genetic instruments is expected to reduce the pleiotropic effect, which is important to ensure that the MR analysis results are robust.

MATERIALS AND METHODS

This study was approved by the respective institutions’ ethical committees (Osaka University and National Defense Medical College). All procedures were performed in accordance with the Declaration of Helsinki, with written informed consent obtained from each participant.

We obtained the Japanese GWAS summary statistics for habitual coffee consumption, defined as the number of days per week that a subject drank coffee (152,634 subjects) (4), gout (3053 cases and 4554 controls) (5), and SUA levels (121,745 subjects) (6), all of which were among the largest studies with non-Europeans. As genetic instruments, we obtained the 11 lead single nucleotide polymorphisms (SNPs) at loci with a genome-wide significance threshold ($P < 5.0 \times 10^{-8}$) in the Japanese GWAS dataset of coffee consumption (Supplementary Table S1). Among these SNPs, rs75544042 was not contained in the Japanese gout GWAS dataset, so we adopted rs141471965 as a proxy SNP, which has a linkage disequilibrium of $r^2 = 1$ in the 1000 Genomes Project phase 3v5 East Asian populations (1KGP p3v5 EAS). The forest plot describing MR effect size for individual SNPs (Figure 1) and the funnel plot (Supplementary Figure S1) showed an apparent outlier SNP (rs141471965 of ABCG2). We therefore excluded rs141471965 and performed MR analysis using 10 instruments. For the same reason, we excluded rs141471965 in the MR analysis between coffee consumption and SUA levels.

For the European analysis, we used summary statistics provided by the Coffee and Caffeine Genetics Consortium (CCGC) (7) as exposure and used Global Urate Genetics Consortium–provided GWAS summary statistics (8) as outcome. In the CCGC...
| Population | Exposure | Outcome  | No. of instruments | Method          | β    | SE     | OR [95% CI]     | P           | Heterogeneity | Pleiotropy |
|------------|----------|----------|--------------------|------------------|------|--------|----------------|-------------|---------------|------------|
|            |          |          |                    |                  |      |        |                |             |               |            |
| Japanese   | Coffee   | Gout     | 10                 | IVW (fixed-effect) | −1.25| 0.08   | 0.29 [0.24-0.34] | 2.5 × 10⁻⁹  | 5.5 × 10⁻¹⁸  | —          |
|            |          |          |                    | IVW (random-effect)| −1.25| 0.29   | 0.29 [0.16-0.51] | 1.9 × 10⁻⁵  | —             | —          |
|            |          |          |                    | MR-Egger         | −1.76| 0.48   | 0.17 [0.07-0.44] | 6.1 × 10⁻⁴  | 1.4 × 10⁻¹⁵  | 0.22        |
|            |          |          |                    | Weighted-median  | −1.40| 0.33   | 0.25 [0.13-0.47] | 2.7 × 10⁻⁵  | —             | —          |
|            |          |          |                    | Weighted-mode    | −1.85| 0.19   | 0.16 [0.11-0.23] | 3.8 × 10⁻⁵  | —             | —          |
| Coffee     | Gout     |          | 7                  | IVW (fixed-effect) | −0.29| 0.13   | 0.75 [0.58-0.97] | 0.026       | 0.39          | —          |
|            |          |          |                    | IVW (random-effect)| −0.29| 0.13   | 0.75 [0.58-0.97] | 0.030       | —             | —          |
|            |          |          |                    | MR-Egger         | −0.34| 0.30   | 0.71 [0.39-1.28] | 0.31         | 0.29          | 0.84        |
|            |          |          |                    | Weighted-median  | −0.27| 0.16   | 0.77 [0.57-1.04] | 0.086       | —             | —          |
|            |          |          |                    | Weighted-mode    | −0.28| 0.16   | 0.76 [0.55-1.04] | 0.14         | —             | —          |
| Coffee     | SUA levels|         | 9                  | IVW (fixed-effect) | −0.080| 0.014 | 0.92 [0.9-0.95] | 9.6 × 10⁻⁹  | 2.0 × 10⁻¹⁶  | —          |
|            |          |          |                    | IVW (random-effect)| −0.080| 0.047 | 0.92 [0.84-1.01] | 0.090       | —             | —          |
|            |          |          |                    | MR-Egger         | 8.0 × 10⁻⁴ | 0.11 | 1.00 [0.81-1.24] | 0.99        | 2.2 × 10⁻¹⁵  | 0.44        |
|            |          |          |                    | Weighted-median  | −0.022| 0.020 | 0.96 [0.94-1.02] | 0.26        | —             | —          |
|            |          |          |                    | Weighted-mode    | −0.011| 0.017 | 0.99 [0.96-1.02] | 0.55        | —             | —          |
| European   | Coffee   | Gout     | 5                  | IVW (fixed-effect) | −0.58| 0.21   | 0.56 [0.38-0.84] | 5.3 × 10⁻³  | 0.027         | —          |
|            |          |          |                    | IVW (random-effect)| −0.58| 0.34   | 0.56 [0.29-1.1]  | 0.092       | —             | —          |
|            |          |          |                    | MR-Egger         | −0.29| 0.83   | 0.75 [0.15-3.8]  | 0.75        | 0.016         | 0.72        |
|            |          |          |                    | Weighted-median  | −0.92| 0.30   | 0.4 [0.22-0.72]  | 2.1 × 10⁻³  | —             | —          |
|            |          |          |                    | Weighted-mode    | −0.98| 0.39   | 0.37 [0.17-0.8]  | 0.065       | —             | —          |
| Coffee     | SUA levels|         | 5                  | IVW (fixed-effect) | −0.15| 0.03   | 0.86 [0.8-0.92]  | 7.9 × 10⁻⁶  | 6.8 × 10⁻⁸  | —          |
|            |          |          |                    | IVW (random-effect)| −0.15| 0.11   | 0.86 [0.7-1.06]  | 0.15        | —             | —          |
|            |          |          |                    | MR-Egger         | −0.16| 0.26   | 0.85 [0.51-1.43] | 0.58        | 1.7 × 10⁻⁸  | 0.97        |
|            |          |          |                    | Weighted-median  | −0.03| 0.05   | 0.97 [0.87-1.07] | 0.51        | —             | —          |
|            |          |          |                    | Weighted-mode    | −0.10| 0.06   | 0.91 [0.81-1.01] | 0.16        | —             | —          |

Abbreviations: IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; SUA, serum uric acid.

a After exclusion of the outlier instruments (rs141471965 on ABCG2) in the forest plot.
b After additional exclusion of the three instruments suspected to have pleiotropy effects.
c IVW (fixed-effect) analyses were previously performed by Larsson et al (2).
GWAS, coffee consumption was defined in terms of cups per day. We adopted five instruments, as did Larsson et al previously.

We used R statistical software with the TwoSampleMR package (9) for MR analysis. We began by performing an IVW analysis using multiple instruments. A \( P \) value of 0.05 by Cochran’s \( Q \) test was used as the threshold for determining whether to prioritize the fixed effects model or the random effects model. We also performed weighted-median, weighted-mode, and MR-Egger analysis to relax the instrumental variable assumption. The three methods adopt individually different strategies to avoid the impact of invalid instruments.

For a more conservative analysis with the Japanese dataset, we additionally excluded the three instruments suspected to have a pleiotropic effect on gout. Matoba et al reported that polymorphisms on \( \text{ALDH} \) have a genetic impact on alcohol drinking behavior as well as on coffee consumption (4). Polymorphisms of \( \text{ALDH} \) therefore may affect gout independently of coffee consumption. Furthermore, Hutton et al reported that the risk alleles of \( \text{GCKR} \) and \( \text{MLXIPL} \) affect gout independently of coffee intake (10). Based on these facts, we removed rs671 (\( \text{ALDH2} \)), rs1260326 (\( \text{GCKR} \)), and rs13234378 (\( \text{MLXIPL} \)) from 10 instruments and reanalyzed using the remaining seven instruments.

As a complementary analysis, we applied Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) (11) to the original 11 lead SNPs to examine whether they had a statistically significant pleiotropic effect.

Finally, we performed a multivariable MR analysis (12) to estimate the association between coffee consumption and gout while adjusting for SUA levels. We performed a multivariable MR analysis in the Japanese population because we were able to access the full summary statistics of coffee consumption in only the Japanese cohort. In the multivariable MR analysis, we also excluded rs141471965 (\( \text{ABCG2} \)), and the three instruments were removed in the aforementioned conservative analysis.

RESULTS

Of the 11 lead SNPs from the Japanese GWAS dataset of coffee consumption, rs141471965 of \( \text{ABCG2} \) was an apparent outlier in the forest plot (Figure 1) and funnel plot (Supplementary Figure S1). A random effect IVW analysis for gout was therefore performed using the remaining 10 instruments (\( P_{\text{het}} = 5.5 \times 10^{-19} \) in Cochran’s \( Q \) test: Table 1, Figure 2) with an \( F \) statistic of 132, indicating that the instruments are sufficiently

![Figure 2](image-url)  

**Figure 2.** Scatter plots describing the association between coffee consumption (exposure) and gout or SUA levels (outcome). Dots represent the coffee-associated SNPs plotted along with effect size estimates on coffee consumption (x-axis) and gout or uric acid levels (y-axis) with 95% confidence intervals (a-c) in Japanese and (d and e) in Europeans. The line slopes indicate the effect size estimates in four MR analyses using multiple SNPs (ie, inverse variance weighted, MR-Egger, weighted-median, and weighted-mode). Each method is indicated by differently colored lines. Prior to each of the analyses, we removed the outlier instrument (rs141471965 of \( \text{ABCG2} \)) in panels a and c and removed the three instruments suspected to have pleiotropic effects on gout in panel b. MR, Mendelian randomization; SNP, single nucleotide polymorphism; SUA, serum uric acid.
associated with coffee consumption to permit us to ignore weak instrument bias. Coffee consumption was significantly inversely associated with gout (odds ratio [OR] = 0.29, 95% confidence interval [95% CI]: 0.16-0.51, \( P = 1.9 \times 10^{-6} \)).

The previous European MR study used fixed-effect IVW analysis despite the significant heterogeneity seen \((P_{\text{het}} = 0.027)\), and we did not obtain a significant result in random effect IVW analysis \((OR = 0.56, 95\% \text{ CI}: 0.29-1.1, P = 0.092)\).

With the Japanese dataset, we also applied weighted-median, weighted-mode, and MR-Egger analysis to eliminate the impact of latent invalid instruments. We confirmed a significant inverse association between coffee consumption and gout in all the methods \((P = 2.7 \times 10^{-5} \text{ in weighted-median, } P = 3.8 \times 10^{-6} \text{ in weighted-mode, and } P = 6.1 \times 10^{-3} \text{ in MR-Egger})\). The intercept analysis in MR-Egger did not indicate any significant directional pleiotropy \((P = 0.22)\). Similar results were obtained with all 11 instrumental variables except for MR-Egger analysis (Supplementary Table S2).

As a conservative analysis, we excluded three more instruments \((rs671 \text{ of } ALDH2, rs1260326 \text{ of } GCKR, \text{ and } rs132234378 \text{ of } MLXIPL)\) suspected to have a pleiotropic effect on gout and analyzed using the remained seven instruments. With this framework, no heterogeneity was supported \((P_{\text{het}} = 0.39)\), and we observed a consistent result of coffee consumption being inversely associated with gout in fixed-effect IVW analysis \((OR = 0.75, 95\% \text{ CI}: 0.58-0.97, P = 0.026)\). As another strategy to test for pleiotropy, we applied MR-PRESSO to the 11 lead SNPs to evaluate whether or not they were outliers. MR-PRESSO revealed \(rs141471965 \text{ (ABCG2)}\) and \(rs4410790 \text{ (AHR)}\) to be statistical outliers. The MR analysis that removed them also supported our result, in which coffee consumption was negatively associated with gout \((OR = 0.21, 95\% \text{ CI}: 0.12-0.35, P = 8.8 \times 10^{-5})\) as random effect IVW analysis \((P_{\text{het}} = 1.4 \times 10^{-13})\).

MR analysis between coffee consumption and SUA levels in both ancestries showed no significant inverse causal association except for fixed-effect IVW analysis, which did not take pleiotropy into account, and from which conclusions should not be drawn because of significant heterogeneity \((P_{\text{het}} = 2.0 \times 10^{-16} \text{ in Japanese and } P_{\text{het}} = 6.8 \times 10^{-8} \text{ in Europeans})\).

Furthermore, our multivariable MR analysis confirmed the independent effect of coffee consumption on gout after adjustment for SUA levels \((OR = 0.50, 95\% \text{ CI}: 0.31-0.81, P = 0.0046)\). These findings suggest that coffee consumption reduces gout risk independently of SUA levels. Coffee consumption thus appears to have protective effects on the progression from asymptomatic hyperuricemia to gout.

**DISCUSSION**

In this study, we performed the first MR analysis for estimating the impact of coffee consumption on SUA levels and gout risk, taking pleiotropy into account. Our findings from the Japanese population are the first to reveal that coffee consumption reduces gout risk, as revealed by MR analyses, whereas our reanalyses of previous datasets from Europeans did not show significant associations between coffee consumption and gout risk. By considering pleiotropy, the present results are more robust than those in the report by Larsson et al. Our robust MR analyses showed significant results from Japanese datasets. The outlier variant of \(rs141471965\) in the 11 genetic instruments is a proxy \((\rho^2 = 1\text{ in }1\text{KGP }p3v5\text{ EAS})\) for \(p\text{.Gln141Lys (rs2231142), the ABCG2 mis}-\text{sense SNP. The rs2231142 variant has been reported to alter the function of the urate transporter, resulting in increased SUA levels and gout risk in various populations, including Japanese (13,14). This fact explains why }rs141471965\text{ has an obvious pleiotropic effect on gout risk not mediated by coffee consumption. A conservative analysis without three more instruments worked well because heterogeneity was not supported by the Cochran’s Q test in the final analysis. The present study suggests the effect of coffee consumption on gout risk to be independent of SUA levels. The previous European MR analysis reported that coffee consumption significantly reduced SUA levels (2), but when heterogeneity was taken into account, the significance was no longer supported. In a systematic review and meta-analysis, Zhang et al reported coffee consumption to significantly reduce the gout risk but not reduce SUA levels (1). A recent observational study has also shown there to be no significant relationship between coffee consumption and SUA levels (15). Nevertheless, the relationship between coffee consumption and SUA levels is still unclear; the present results may suggest that coffee consumption reduces gout risk independently of uric acid, possibly acting against inflammation and/or innate immunity (16).

One of the limitations of this study is that in the Japanese MR analysis, we used as exposure the number of days per week that a subject drank coffee, because it was the only available data collected by questionnaire. The loci identified in the Japanese and European coffee consumption GWAS were mostly concordant (Supplementary Table S1), and we conclude that the genetic effects of each study reflect the same biological pathway. However, because data collected in different study designs can be a source of disjoint effects on outcome, a further study needs to be conducted to elucidate the mechanism by which coffee consumption protects against the development of gout.

In summary, by MR analyses using large-scale GWAS results across ancestry populations and by considering the heterogeneity and pleiotropy of instruments, our study indicates that coffee consumption can causally reduce gout risk. Although the impact on SUA levels is still ambiguous, obvious protective effects of habitual coffee consumption on gout risk were observed. We consider that coffee consumption may reduce gout risk independently of SUA levels. Our study suggests the presence of biological pathways involved in gout pathogenesis other than SUA levels and should contribute to the development of preventive medicine against gout.
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AUTHOR CONTRIBUTORS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Okada and Matsuo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDIX A

Members of the Japan Gout Genomics Consortium (Japan Gout) are as follows: Kinyaoshi Ichida, Tappei Takada, Hirofumi Nakaoka, Ken Yamamoto, Tony R. Merriman, Takahiro Nakamura, the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study Group (principal investigator: Kenji Wakai), Toru Shimizu, Hiroshi Ooyama, Keiko Ooyama, Mitsuo Nagase, Yuji Hidaka, Satoko Suzuki, Satoko Iwasawa, Hiroshi Nakashima, Yutaka Sakurai, and Masashi Tsunoda.