Causal Association Between Tea Consumption and Gout: A Mendelian Randomization Study*

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[Abstract] Objective: Evidence from prospective studies on the consumption of tea and risk of gout is conflicting and limited. We aimed to investigate the potential causal effects of tea intake on gout using Mendelian randomization (MR). **Methods:** Genome-wide association studies in UK Biobank included 349 376 individuals and successfully discovered single-nucleotide polymorphisms linked to consumption of one cup of tea per day. Summary statistics from the Chronic Kidney Disease Genetics consortium included 13 179 cases and 750 634 controls for gout. Two-sample MR analyses were used to evaluate the relationship between tea consumption and gout risk. The inverse-variance weighted (IVW) method was used for primary analysis, and sensitivity analyses were also conducted to validate the potential causal effect. **Results:** In this study, the genetically predicted increase in tea consumption per cup was associated with a lower risk of gout in the IVW method (OR: 0.90; 95% CI: 0.82–0.98). Similar results were found in weighted median methods (OR: 0.88; 95% CI: 0.78–1.00), while no significant associations were found in MR-Egger (OR: 0.89; 95% CI: 0.71–1.11), weighted mode (OR: 0.80; 95% CI: 0.65–0.99), and simple mode (OR: 1.01; 95% CI: 0.75–1.36). In addition, no evidence of pleiotropy was detected by MR-Egger regression (P=0.95) or MR-PRESSO analysis (P=0.07). **Conclusion:** This study provides evidence for the daily consumption of an extra cup of tea to reduce the risk of gout.
Key words: tea consumption; gout; single-nucleotide polymorphisms; Mendelian randomization

Gout is the most prevalent type of inflammatory arthritis globally, affecting approximately 41 million individuals according to the latest estimates from the Global Burden of Disease study[1]. Regrettably, despite a solid understanding of the underlying mechanisms and the wide availability of treatment options, the prevalence of gout remains high, and the management of the condition continues to be less than ideal[2]. The high prevalence of comorbidities among gout patients, including hypertension (75%), chronic kidney disease (CKD) (70%), obesity (53%), and cardiovascular disease (10%–14%), contributes to the overall burden of the disease, leading to an increased risk of morbidity and mortality[3]. While medicinal management principles have been effectively applied to clinical practice[4], dietary adjustments and lifestyle changes are also recommended for individuals with gout. Poor diet and lifestyle choices, which lead to obesity and diabetes and are associated with affluence, have been shown to significantly increase the risk of developing gout[4–6]. Several epidemiological studies across various countries have indicated a rise in both the prevalence and incidence of gout in recent decades, which can be attributed to changes in lifestyle factors that increase the risk of gout[7, 8]. In recent times, many studies, such as the Health Professionals Follow-up Study and Third National Health and Nutrition Examination Survey, have provided substantial evidence linking lifestyle factors, hyperuricemia with gout, which were hypothesized previously only[9–20]. The results of these studies have validated the notion that certain dietary habits contribute to an increased risk of hyperuricemia

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and gout. New factors that were previously not part of conventional lifestyle guidelines have been discovered. These include harmful factors, such as fructose and sugar-sweetened beverages[19, 21–23], and beneficial factors, such as coffee consumption[17, 23] and vitamin C supplementation[13, 18, 24].

Tea ranks among the top most favored beverages globally[25]. A few studies have been conducted on the correlation between tea consumption and the risk of developing gout, with only limited research examining this association[26–29]. However, the results of these studies were inconclusive and inconsistent in establishing a strong association between tea intake and gout risk. The inconsistency in the findings could be attributed to differences in tea varieties (such as green, black, and oolong tea) as well as demographic diversity (such as sex)[30]. A prospective cohort study indicated that those who consumed tea daily had a strong nonlinear association with reduced gout risk[29]. However, two prospective cohort studies found no significant correlation between tea consumption and the risk of gout[26, 27]. Further research is required to examine the impact of tea consumption on gout in light of the variability in prior studies and the use of different metrics. Moreover, due to the constraints of research and likelihood of confounding variables or reverse causation in traditional epidemiological studies, it cannot be definitively established whether there exists a causal connection between tea consumption and gout. Thus, the causal association between tea consumption and gout remains uncertain.

The Mendelian randomization (MR) approach is a genetic epidemiology design that increases the accuracy of drawing causal conclusions by utilizing genetic variants as instrumental variables (IVs) to represent exposure (e.g., tea intake) and predict outcomes (e.g., gout)[31]. At the start, single nucleotide polymorphism (SNP) sites are assigned randomly, thereby reducing the likelihood of reverse causation and residual confounding biases[32]. The causal relationship between tea consumption and gout has not yet been investigated. In this study, the two-sample MR approach was applied to assess the causal association between tea consumption and gout.

1 MATERIALS AND METHODS

1.1 Genetic Instrument Selection

The UK Biobank-based Genome-Wide Association Study (GWAS) Summary dataset for Tea Consumption (phenotypic code: 1488_raw), which includes more than 349 376 samples of European ancestry, was downloaded from Neale Lab (http://www.nealelab.is/uk-biobank) (GWAS Round 2). Specifically, UK Biobank is a large-scale cohort study that includes individuals between the ages of 40 and 69 years who reside in the United Kingdom. The GWAS was controlled for 6 variables, namely sex, age, age squared, sex-age interaction, sex-age product, and the initial 20 principal components of ancestry. Data on habitual tea consumption were obtained from dietary questionnaires. For instance, one question was: "How many cups of tea (including black and green) do you drink every day?" GWAS summary data of unconverted daily tea intake were employed to pinpoint SNPs related to the habit of drinking tea. Comprehensive information about the phenotype and quality control process was employed in the UK Biobank on the Neale Lab website (https://github.com/Nealelab/UK_Biobank_GWAS).

After applying a significance threshold of $P<5\times10^{-8}$ and filtering for minor frequency >1%, we obtained 2672 distinct autosomal biallelic SNPs that underwent additional quality control procedures. To ensure the independence of the selected genetic variants, we used European sample reference data from the 1000 Genomes Project[33] to perform clumping of the 2672 SNPs with linkage disequilibrium $r^2<0.001$ within a 10 000 kb window. Finally, 45 SNPs were found to be independently associated with tea consumption. The R^2 value was used to estimate the proportion of variance in tea consumption explained by each of the 45 SNPs[34], while the instrumental strength of each SNP was evaluated through the F-statistic[35].

1.2 Genetic Summary Data of Gout

We obtained summary statistics for gout from the Chronic Kidney Disease Genetics (CKDGen) consortium, which is the largest available GWAS and is comprised of multiple European-ancestry cohorts. The dataset contains 13 179 cases and 750 634 controls for gout[36]. The diagnosis of gout cases was made using self-reported information, the use of urate-lowering medications, or identification of specific International Statistical Classification of Diseases (ICD) and Related Health Problems codes related to gout. All summary data are available from the Open GWAS Project database of the UK Medical Research Council's Integrated Epidemiology Unit.

All study analyses are based on publicly available GWAS aggregate statistics (http://gwas.mrcieu.au.uk) and do not require additional ethical approval or informed consent.

1.3 Statistical Analyses

To infer the potential causal relationship between gout and tea intake, we carried out a two-sample MR analysis. The MR study relied on 3 fundamental assumptions: (1) closely associated with tea intake; (2) not associated with confounders of the association between tea intake and gout; and (3) can only affect the outcome through exposure without other pathways[37, 38]. Weak instrumental variables were tested by F-statistics: F-statistics=$(N-k-1)/k\times R^2/(1-R^2)$, where N is the sample size, k is the number of genetic instruments, and

R^2 is the genetic instrument explaining the variance in tea consumption. In the MR study, F>10 proved to be a powerful genetic tool. We primarily utilized the inverse variance weighted (IVW) method for the MR analysis, which yielded a reliable estimation of the relationship between the exposure and probability of developing outcomes in the absence of pleiotropic IVs[39]. To evaluate the heterogeneity among individual SNPs, we calculated Cochran's Q statistics. A fixed-effects model was employed if there was no significant heterogeneity (P<0.05). Alternatively, we used a random-effects model[40]. The sensitivity analysis was performed to ensure the stability and reliability of our findings. The weighted median method was utilized because it can produce a reliable estimation of the overall effect when more than 50% of IVs are valid, which can minimize the bias in the causal effect estimation in comparison to the IVW method[41]. "Leave-one-out" analyses were performed to determine whether any single SNP could cause a causal association. The validity of the relationship between the chosen SNPs and exposures was confirmed through the use of the PhenoScanner database5 (table S1). SNPs that displayed an association with traits other than tea consumption were noted at a statistical significance level of $P<5\times10^{-8}$.

Furthermore, the MR-Egger approach is a modification of Egger regression, which addresses directional pleiotropy by adding an intercept term in the weighted regression model. If the value of the intercept term deviates from 0, it suggests the presence of horizontal pleiotropy[42]. In addition, the MR pleiotropy residual sum and outlier test (MR-PRESSO) method was used to identify and adjust for multiple effects by eliminating potential outliers[43].

All statistical analyses were performed using "Sample MR" and "MRPRESSO" packages in R software version 4.2.2. P values of <0.05 were considered to indicate statistical significance.

2 RESULTS

2.1 Causal Association Between Tea Consumption and Gout

A threshold of F-statistics >10 suggests that the genetic variants have significant and robust estimated effects in the MR analyses. Table 1 shows the details of the relationship between the selected SNPs and exposure. Table 2 displays the results of MR analyses regarding the estimated causal effect of tea consumption on the development of gout. In the IVW MR analyses, we observed that the OR of gout associated with an increase of one cup of tea per day was 0.897 (95% CI: 0.818–0.983; P=0.020). The leave-one-out analysis failed to identify any SNPs that might have a disproportionate impact on the outcome. The estimated values obtained from the weighted median analysis (OR: 0.884; 95% CI: 0.783–0.998; P=0.046) were consistent and of similar magnitude to the previous results. The results generated by the MR-Egger analysis (OR: 0.891; 95% CI: 0.712–1.115; P=0.320) did not achieve statistical significance, indicating that the effectiveness of the intervention may be limited, and the results should be interpreted with caution. Fig. 1 illustrates the scatter plot of SNP-gout associations compared to SNP-tea associations. Additionally, fig. 2 presents the forest plots of tea-gout estimations for each SNP (table S2).

2.2 Sensitivity Analyses

The IVW test (P=0.073) and MR-Egger (P=0.09) showed no indication of heterogeneity among the IV estimates derived from the individual variants of gout. The MR-Egger regression analysis yielded an Egger intercept of 0.0004 (P=0.953), which suggests an absence of pleiotropy. Meanwhile, the MR-PRESSO method revealed a P value of 0.073, indicating no significant horizontal pleiotropy. The "leave-one-out" analysis revealed that no individual SNP significantly influenced the IVW point estimate (fig. 3, table S3). Although these approaches suggest no heterogeneity, according to table S1, other exposure factors (e.g., hypertension, weight, self-reported high cholesterol, uric acid) of the selected SNPs may have some association with gout. We repeated the MR analysis after removing these 5 SNPs, and the results were similar to the previous MR analysis except that the P value for the weighted mode became significant (table S4).

3 DISCUSSION

This two-sample MR study utilized summary-level data from the UK Biobank and CKDGen consortium to assess the likely causal relationship between tea consumption and the risk of developing gout. The UK Biobank dataset yielded a total of 2672 SNPs that were linked to tea consumption. Based on the consistent results observed in various sensitivity analyses, it can be inferred that consuming tea may have an impact on individuals with gout.

The relationship between gout risk and tea consumption has not been consistently observed in previous studies. In a large cohort of 45 869 adult men, tea intake was not associated with the risk of gout during a 12-year period[26]. In the Nurses' Health Study, including 89 433 female participants over a 26-year period, tea consumption was not significantly associated with the risk of gout[27]. However, in another prospective cohort study, including 447 658 participants in the UK Biobank, high tea intake (>at least 6 cups/day) had a strong declining nonlinear association with gout risk[29]. Our study found that genetically predicted tea intake was causally associated with a decrease

Table 1 Characteristics of SNPs associated with tea consumption

SNPs	Position	EAF	EA	NEA	BETA	SE	*P*	*N*	R^2	*F*-statistic
rs1030510	7:17100273	0.45	G	A	–0.0436	0.0069	3.60E–10	349 376	0.000114	40
rs10741694	11:16286183	0.63	C	T	0.0404	0.0071	1.53E–08	349 376	0.0000927	32
rs11022751	11:13307613	0.27	C	T	0.0497	0.0078	1.83E–10	349 376	0.000116	41
rs112476491	7:17204040	0.03	A	G	–0.1186	0.0194	8.88E–10	349 376	0.000107	37
rs11487328	1:174601659	0.38	C	G	–0.0493	0.0071	5.16E–12	349 376	0.000138	48
rs11636222	15:75515312	0.23	G	T	–0.0557	0.0089	3.79E–10	349 376	0.000112	39
rs12591786	15:60902512	0.16	T	C	–0.0609	0.0096	2.32E–10	349 376	0.000115	40
rs12600469	17:40834073	0.62	T	G	0.0406	0.0071	1.22E–08	349 376	0.0000936	33
rs12901092	15:75374145	0.39	A	C	–0.0654	0.0071	3.20E–20	349 376	0.000243	85
rs12916473	15:75321999	0.04	A	G	0.1233	0.0185	2.63E–11	349 376	0.000127	44
rs140775622	20:62962869	0.17	T	C	0.0707	0.0099	9.33E–13	349 376	0.000146	51
rs1481012	4:89039082	0.11	G	A	–0.0778	0.0109	9.41E–13	349 376	0.000146	51
rs149375687	5:152034989	0.27	T	G	–0.0449	0.0078	7.26E–09	349 376	0.0000948	33
rs1601409	12:17066769	0.46	G	A	0.0382	0.0069	3.67E–08	349 376	0.0000877	31
rs1669433	12:11349732	0.84	G	A	0.0551	0.0093	3.33E–09	349 376	0.0001	35
rs17645813	7:17419697	0.08	A	G	–0.1058	0.013	3.32E–16	349 376	0.00019	66
rs199621380	1:150700614	0.41	G	T	0.0413	0.007	4.53E–09	349 376	0.0000996	35
rs200062544	7:17260246	0.47	A	G	0.049	0.007	2.64E–12	349 376	0.00014	49
rs2315024	19:19423817	0.33	A	T	0.0434	0.0073	2.98E–09	349 376	0.000101	35
rs2465018	6:51241140	0.23	A	G	0.0635	0.0082	1.38E–14	349 376	0.000172	60
rs2472297	15:75027880	0.27	T	C	0.1576	0.0078	3.82E–91	349 376	0.00117	408
rs28548701	15:74346021	0.8	C	T	–0.0502	0.0086	5.82E–09	349 376	0.0000975	34
rs28676340	15:75449794	0.16	G	A	–0.0564	0.01	1.96E–08	349 376	0.000091	32
rs34591452	15:74492585	0.24	T	G	0.0759	0.0081	5.48E–21	349 376	0.000251	88
rs34606716	7:75820449	0.24	A	G	–0.0453	0.0082	2.70E–08	349 376	0.0000873	31
rs3815455	7:75611756	0.29	T	C	0.0647	0.0076	1.74E–17	349 376	0.000207	72
rs397074	15:74599997	0.31	C	G	–0.0521	0.0075	2.80E–12	349 376	0.000138	48
rs4410790	7:17284577	0.63	C	T	0.1215	0.0072	1.89E–64	349 376	0.000814	285
rs4817505	21:34343828	0.39	C	T	0.0411	0.0071	6.22E–09	349 376	0.0000959	34
rs4887165	15:74889356	0.81	C	T	0.0539	0.0089	1.22E–09	349 376	0.000105	37
rs60223362	7:17459648	0.2	C	T	–0.0747	0.0086	5.35E–18	349 376	0.000216	75
rs6495129	15:75196717	0.2	T	G	–0.0582	0.0086	1.35E–11	349 376	0.000131	46
rs6697410	1:26756209	0.74	T	G	0.0436	0.0079	4.10E–08	349 376	0.0000872	30
rs6965666	7:17177312	0.28	C	T	–0.0503	0.0078	9.14E–11	349 376	0.000119	42
rs7174381	15:75613289	0.31	C	A	0.0522	0.0075	3.85E–12	349 376	0.000139	48
rs73071153	7:17545964	0.03	A	G	–0.1312	0.0194	1.32E–11	349 376	0.000131	46
rs73075157	7:17566844	0.13	A	G	–0.0678	0.0103	5.42E–11	349 376	0.000124	43
rs73169830	22:24885208	0.08	C	T	0.1027	0.0131	3.81E–15	349 376	0.000176	61
rs73424602	22:41461176	0.4	T	C	–0.0432	0.007	7.84E–10	349 376	0.000109	38
rs77821156	7:17331450	0.11	G	A	0.0643	0.0113	1.39E–08	349 376	0.0000927	32
rs79217743	15:75117912	0.14	T	G	–0.0602	0.0102	3.34E-09	349 376	0.0000997	35
rs79413667	7:17399486	0.03	G	C	–0.1171	0.0201	6.03E–09	349 376	0.0000971	34
rs79694830	7:17286087	0.06	T	C	0.0951	0.015	2.26E–10	349 376	0.000115	40
rs7999399	13:89233505	0.55	T	C	0.0379	0.0069	4.96E–08	349 376	0.0000863	30
rs9624470	22:24820268	0.58	A	G	0.0729	0.007	3.06E–25	349 376	0.00031	108

EA: effect allele; EAF: effect allele frequency; NEA: non effect allele; SE: standard error; SNP: single nucleotide polymorphism. R^2 was calculated as follows: $2\times beta^2\times EAF\times(1–EAF)/[2\times beta^2\times EAF\times(1–EAF)+SE^2\times2\times N\times EAF\times(1–EAF)]$. The *F*-statistic for each SNP was calculated as follows: $F=(N–2)\times R^2/(1–R^2)$.

Table 2 The results of MR analyses

Outcome	Exposure	Method	SNPs	BETA	SE	OR	95%CI	*P*
Gout	Tea consumption	MR Egger	35	–0.115	0.114	0.891	(0.712, 1.114)	0.320
Gout	Tea consumption	Weighted median	35	–0.123	0.062	0.884	(0.783, 0.998)	0.046
Gout	Tea consumption	Inverse variance weighted	35	–0.109	0.047	0.897	(0.818, 0.983)	0.020
Gout	Tea consumption	Simple mode	35	0.009	0.152	1.009	(0.749, 1.360)	0.952
Gout	Tea consumption	Weighted mode	35	–0.217	0.108	0.805	(0.651, 0.994)	0.052

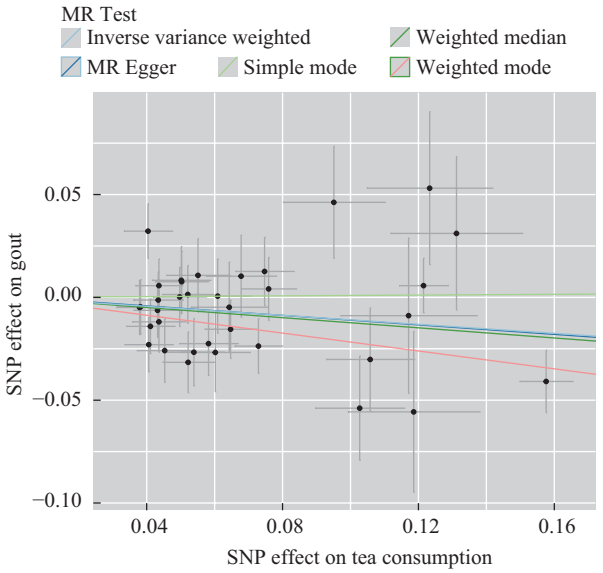

Fig. 1 A scatter plot is used to visualize the causal effect between tea consumption and gout

in gout. This MR study, in which a large number of individuals were from two sample designs, avoided confounding bias and reverse causality.

Although there is no definitive understanding of the exact mechanisms, various pathways have been suggested to elucidate the correlation between the consumption of tea or coffee and the decreased likelihood of developing gout. The primary reason for the positive impact of tea on health is attributed to its bioactive components, such as polyphenols, alkaloids, pigments, and free amino acids[44]. These constituents constitute approximately 18%–36%, 3%–5%, 0.3%–2%, and 2%–4% of the dry weight of tea leaves, respectively[45, 46]. According to animal studies, tea extracts possess three important properties that are crucial in the development of gout[44]: inhibition of xanthine oxidase[47], anti-inflammatory action[48], and effective hypoglycemic effects[49]. The primary chemical constituents of tea are phenolic compounds,

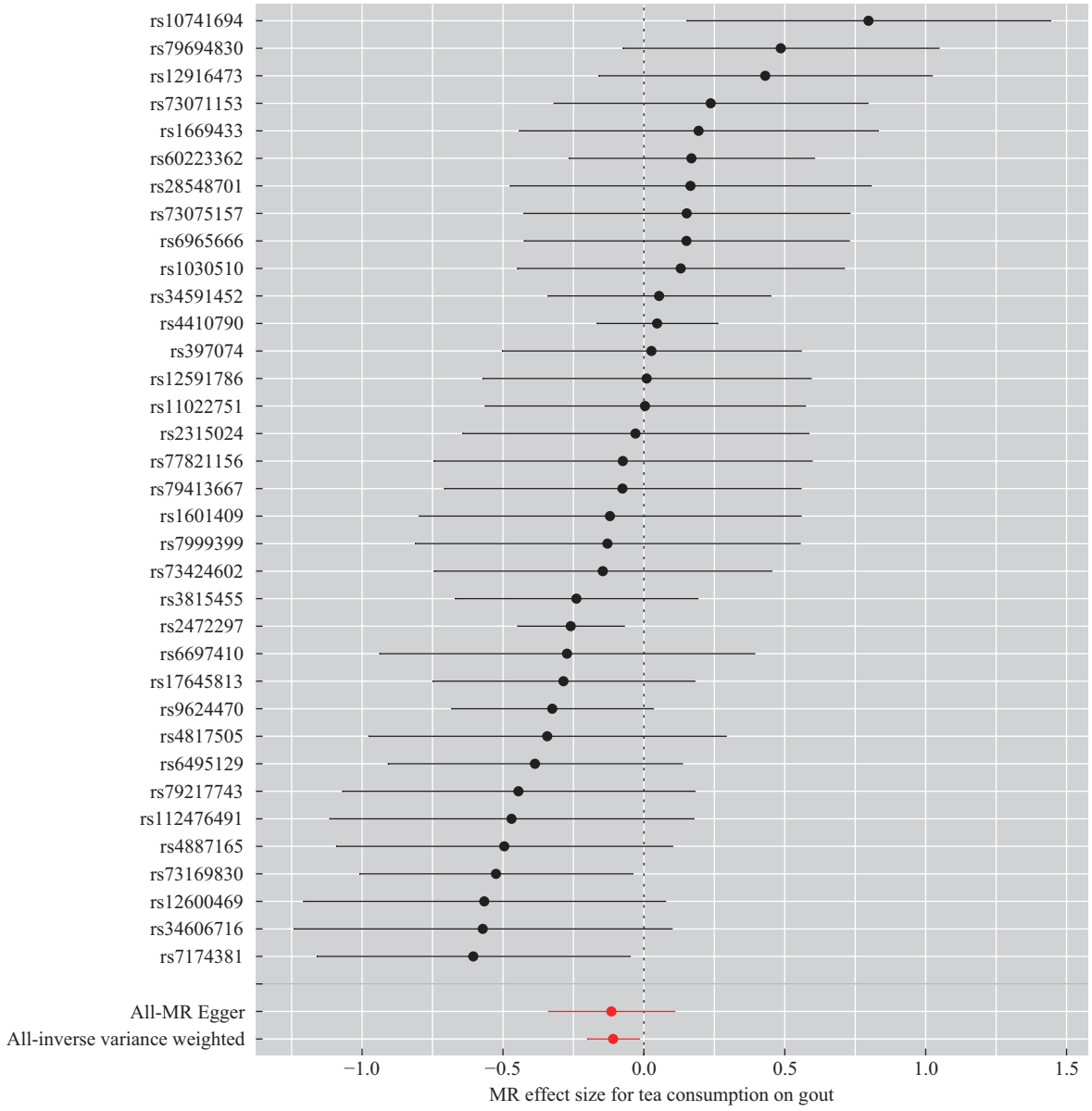

Fig. 2 Forest plots of the causal effects between tea consumption-associated SNPs and risk of gout

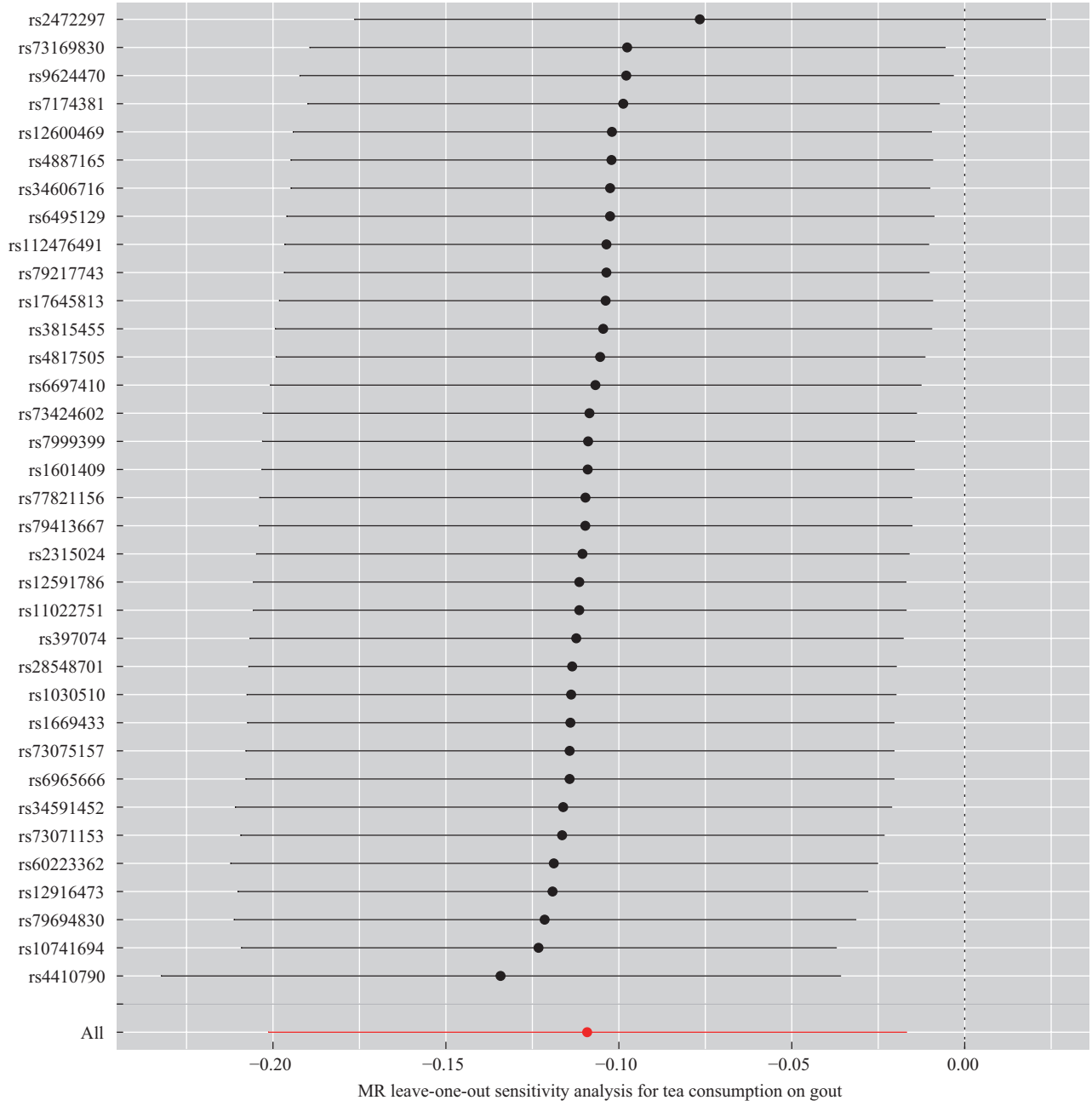

Fig. 3 Forest plot of the "leave-one-out" sensitivity analysis method to show the influence of individual SNPs on the results
The red point indicates the IVW estimates using all SNPs.

particularly tea catechins[50]. The liver enzyme xanthine oxidase can be inhibited by five tea catechins[51].

The primary benefit of this research is the utilization of the two-sample method, which employs a vast collection of genetic data at the summary level and eliminates the possibility of confounding factors and reverse causality found in observational studies. Furthermore, a notable advantage is that the consumption of tea was genetically predicted using data from a comprehensive GWAS of 349 376 individuals of European descent, which effectively reduced the impact of weak instrumental biases (F-statistic >10). Nevertheless, there are certain limitations to this study. First, the findings cannot be generalized to other populations due to the limited data from European populations. Second, the summary-level data used in the study did not allow for the identification of nonlinear relationships or stratification effects. Third, it is significant to acknowledge that our study primarily relied on the existing GWAS data. Since there is a lack of GWAS specifically focused on various types of tea, it becomes challenging to deduce the distinct impacts of tea variants on the causal association between tea consumption and gout. Furthermore, we were unable to identify sex-specific genetic IVs for tea consumption in the currently accessible GWAS data. In future GWAS research investigating the relationship between tea consumption and gout, it is essential to differentiate between male and female participants.

To a certain extent, it could be inferred that

increasing tea consumption by one additional cup per day is causally related to a decreased risk of gout. The comprehensive and meticulous MR analysis undertaken in this study has generated weak evidence that supports the use of tea consumption as a means of preventing and managing gout. Further large studies should be conducted to confirm the causal effect.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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