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# Testing relationship between tea intake and the risk of rheumatoid arthritis and systemic lupus erythematosus: a Mendelian randomization study

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## Abstract

**Background** We performed Mendelian randomization (MR) to assess the causal effect of tea intake on rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

**Methods** Genetic instruments for tea intake were obtained from a large genome-wide association study (GWAS) dataset of the UK Biobank. Genetic association estimates for RA (6236 cases and 147,221 controls) and SLE (538 cases and 213,145 controls) were obtained from the FinnGen study through the IEU GWAS database.

**Results** MR analyses using the inverse-variance weighted method showed that tea intake was not associated with risk of RA [odds ratio (OR) per standard deviation increment in genetically predicted tea intake = 0.997, 95% confidence interval (CI) 0.658–1.511] and SLE (OR per standard deviation increment in genetically predicted tea intake = 0.961, 95% CI 0.299–3.092). Weighted median, weighted mode, MR-Egger, leave-one-out and multivariable MR controlling for several confounding factors including current tobacco smoking, coffee intake, and alcoholic drinks per week yielded completely consistent results. No evidence of heterogeneity and pleiotropy was found.

**Conclusion** Our MR study did not suggest a causal effect of genetically predicted tea intake on RA and SLE.

**Keywords** Mendelian randomization, Rheumatoid arthritis, Systemic lupus erythematosus, Tea intake

## Introduction

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are two common immune mediated inflammatory disorders. RA affects approximately 0.5–1% of the global population, characterized by symmetrical polyarthritis, chronic synovial inflammation, gradual joint deterioration, and chronic disability [1]. SLE can affect both sexes and all ethnicities [2]. The hallmark of SLE includes the production of autoantibodies, aberrant formation of immune complexes, increased levels of pro-inflammatory cytokines, and chronic inflammation of multiple organ systems [3]. The pathogenesis of RA and SLE is complex. Genetic, environmental, and lifestyle factors can affect the risk of RA and SLE. Although lifestyle factors such as alcohol drinking and cigarette smoking have been extensively studied, the effect of tea intake on the risk of RA and SLE remains largely unknown.

Tea is one of the most commonly consumed beverages all over the world. It consists of a number of bioactive compounds including polyphenols and caffeine. These compounds possess antioxidative, anti-inflammatory,

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immunosuppressive, and cancer-preventative properties [4–7]. Some experimental studies showed that tea and its active ingredients such as epigallocatechin-3-gallate (EGCG) could ameliorate animal models of RA by regulating Th17/Treg balance, inducing B cell apoptosis, decreasing pro-inflammatory cytokine production, and inhibiting proliferation of activated synovial fibroblasts [8–11]. Evidence from experimental studies also demonstrated that tea extract alleviated experimental lupus nephritis through promotion of the nuclear factor E2-related factor 2 signaling pathway, inhibition of renal nucleotide-binding domain-like receptor protein 3 activation, and regulation of systemic regulatory T-cell activity [12]. However, observational clinical studies evaluating the association of tea intake with RA and SLE have yielded inconsistent results [13–19].

Mendelian randomization (MR) is an analytical method applying genetic variants as instrumental variables to examine causal associations from observational data. Genetic variants are randomly distributed at conception based on Mendel's law. MR analyses are thus less susceptible to possible confounding factors and reverse causation. In the epidemiology field, MR is increasingly used for assessing the causal effect of a risk or protective factor on an outcome. Prior MR studies have evaluated the causal relationships of several lifestyle factors such as coffee intake, alcohol drinking, and smoking with the risk of RA and SLE [20–24], whereas the role of tea intake remains unclear. In the present study, we applied a two-sample MR approach to assess the causal effect of genetically predicted tea intake on the risk of RA and SLE.

## Methods

Two-sample MR was performed using summary-level data from published genome-wide association studies (GWASs). Ethical approval was not necessary for this MR study; we did not use individual-level data.

### Genetic data for exposures

The GWAS summary statistics for tea intake in individuals of European ancestry (447,485 participants) based on the UK Biobank were obtained from the IEU GWAS database at https://gwas.mrcieu.ac.uk/datasets/ukb-b-6066/. Briefly, the UK Biobank is a large prospective cohort of more than 500,000 participants (aged 40 to 69 years); they were recruited across England, Wales, and Scotland between 2006 and 2010 [25]. As part of the UK Biobank diet Survey, self-reported tea intake was ascertained using a touchscreen question: "How many cups of tea do you drink each day? (include black and green tea)" Participants who answered > 99 or < 0 were excluded, and those answering > 20 were asked to confirm. Genotyping of the participants was undertaken using Affymetrix UK Biobank Axiom array and imputed against the UK10K, 1000 Genomes Phase 3 and Haplotype Reference Consortium panels [26]. The GWAS was adjusted for age, sex, genotyping array, and the principal components by the original GWAS researchers.

Single nucleotide polymorphisms (SNPs) that strongly associated with tea intake at genome-wide significance ($P < 5 \times 10^{-8}$) were selected as instrumental variables. Before performing MR analyses, SNP instruments were clumped at $r^2 < 0.001$ using the R package "TwoSampleMR" version 0.5.6 (https://github.com/MRCIEU/TwoSampleMR). In addition, palindromic SNPs with intermediate allele frequencies were removed. Additional file 1: Table S1 shows the information on genetic variants included as instruments for tea intake.

Current tobacco smoking summary-level data were derived from the Medical Research Council-Integrative Epidemiology Unit (MRC-IEU) consortium (462,434 participants), which is available at https://gwas.mrcieu.ac.uk/datasets/ukb-b-223/. Summary statistics for alcoholic drinks per week were obtained from the GWAS and Sequencing Consortium of Alcohol and Nicotine use (335,394 participants) at https://gwas.mrcieu.ac.uk/datasets/ieu-b-73/ [27]. Genetic instruments for coffee intake were derived from the MRC-IEU consortium (428,860 participants) at https://gwas.mrcieu.ac.uk/datasets/ukb-b-5237/. All data used were from individuals of European ancestry. Additional file 2: Table S2, Additional file 3: Table S3 and Additional file 4: Table S4 show the information on genetic variants included as instruments for current tobacco smoking, alcoholic drinks per week, and coffee intake.

### Genetic data for outcomes

The association of genetic instruments with RA was retrieved from the FinnGen study (6236 RA cases and 147,221 controls) at https://gwas.mrcieu.ac.uk/datasets/finn-b-M13_RHEUMA/. The association of genetic instruments with SLE was also obtained from the FinnGen study (538 SLE cases and 213,145 controls), which is available at https://gwas.mrcieu.ac.uk/datasets/finn-b-M13_SLE/. Launched in 2017, the FinnGen study is a nationwide cohort study which aims to collect and analyze genome and health data from 500,000 Finnish biobank participants. RA and SLE were identified according to International classification of diseases (ICD) codes retrieved from nationwide registries in Finland. Genetic associations in FinnGen were evaluated with adjustment for age, sex, genotype batch, and 10 principal components by the FinnGen researchers. Linkage disequilibrium proxies ($r^2 > 0.8$) were applied if the SNP instruments were missing from the outcome dataset. We

harmonised the exposure and outcome datasets to ensure that the genetic associations reflect the same effect allele.

### Statistical analysis

Our MR study is based on three key assumptions (Additional file 5: Figure S1). To assess if the SNP instruments obtained were robustly associated with tea intake, we calculated the F statistic as previously described by Noyce and colleagues [28]. We considered an F-statistic of more than 10 as sufficient to conduct MR analyses, which is conventionally accepted in the field [29]. In the main MR analyses, we combined the causal estimates for all instrumental variables with the use of the inverse-variance weighted method. It provides reliable causal estimates when directional pleiotropy is absent [30]. To assess the robustness of our main MR results to pleiotropy, the weighted median, weighted mode, MR-Egger, and MR pleiotropy residual sum and outlier (MR-PRESSO) methods were used in sensitivity analyses. The weighted median method can provide a robust evaluation as long as at least 50% of the weight stems from valid instruments satisfying the MR assumptions [31]. The weighted mode method can estimate the causal relationship allowing for even the majority of instrumental variables to be pleiotropic [32]. The MR-Egger approach may be used even though all genetic variants are invalid instrumental variables [30]. We estimated the average directional pleiotropy across instrumental variables with the intercept *P* value of the MR-Egger regression. The MR-PRESSO method (https://github.com/rondolab/MR-PRESSO) can detect horizontal pleiotropic outliers [33]. Besides these robust methods, to minimize any possible confounding introduced by individual SNPs, a leave-one-out analysis was conducted in our sensitivity checks. To look for signs of heterogeneity, Cochran's Q statistic and $I^2$ were calculated [34].

To further control for potential pleiotropic effects, a multivariable MR was carried out [35]. We took into account several covariates including current tobacco smoking, alcoholic drinks per week, and coffee intake. The inverse-variance weighted method was used for multivariable MR. All statistical tests were two sided. All MR analyses were undertaken using R software version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

As shown in Additional file 1: Table S1, among genetic variants included as instruments for tea intake, rs2472297 has the strongest association with tea intake ($P = 2.30 \times 10^{-109}$). The 40 SNPs for tea intake corresponded to a F-statistic of 62.99, explaining 0.56% of the variance in tea intake. In the primary MR analyses, tea intake was not associated with risk of RA (OR per standard deviation increment in genetically predicted tea intake = 0.997, 95% CI 0.658–1.511, $P = 0.988$) and SLE (OR per standard deviation increment in genetically predicted tea intake = 0.961, 95% CI 0.299–3.092, $P = 0.947$) using the inverse-variance weighted method (Table 1 and Fig. 1). The MR-Egger, weighted median and weighted mode MR estimates yielded similar results to the inverse-variance weighted analyses (Table 1 and Fig. 1), suggesting that genetically predicted tea intake was not causally associated with RA and SLE. In the main MR analyses, we found absence of heterogeneity across the individual MR estimates derived from the 40 SNPs (tea intake and RA: Q-statistic = 49.267, $P = 0.126$; tea intake and SLE: Q-statistic = 39.853, $P = 0.432$). The MR-Egger intercept test indicated no evidence of directional pleiotropy (tea intake and RA: intercept of 0.003, $P = 0.724$; tea intake and SLE: intercept of 0.007, $P = 0.775$) (Table 1). In addition, using the MR-PRESSO method, we did not find the presence of pleiotropy (tea intake and RA: *P*-value global

**Table 1** Univariable MR estimates of genetically predicted tea intake on the risk of rheumatoid arthritis and systemic lupus erythematosus

| Exposure | Outcome | Number of instruments | MR method | OR | Association 95% CI | *P* value | Pleiotropy Egger intercept | *P* value | Heterogeneity Q−statistic | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| Tea intake | Rheumatoid arthritis | 40 | Inverse-variance weighted | 0.997 | 0.658–1.511 | 0.988 | | | 49.267 | 0.126 |
| | | | MR—Egger | 0.859 | 0.341–2.162 | 0.748 | 0.003 | 0.724 | 49.103 | 0.107 |
| | | | Weighted median | 0.770 | 0.422–1.403 | 0.393 | | | | |
| | | | Weighted mode | 0.880 | 0.429–1.805 | 0.728 | | | | |
| Tea intake | Systemic lupus erythematosus | 40 | Inverse-variance weighted | 0.961 | 0.299–3.092 | 0.947 | | | 39.853 | 0.432 |
| | | | MR—Egger | 0.685 | 0.051–9.154 | 0.776 | 0.007 | 0.775 | 39.766 | 0.391 |
| | | | Weighted median | 0.407 | 0.069–2.396 | 0.320 | | | | |
| | | | Weighted mode | 0.475 | 0.072–3.145 | 0.445 | | | | |

*CI* confidence interval, *OR* odds ratio, *MR* Mendelian randomization

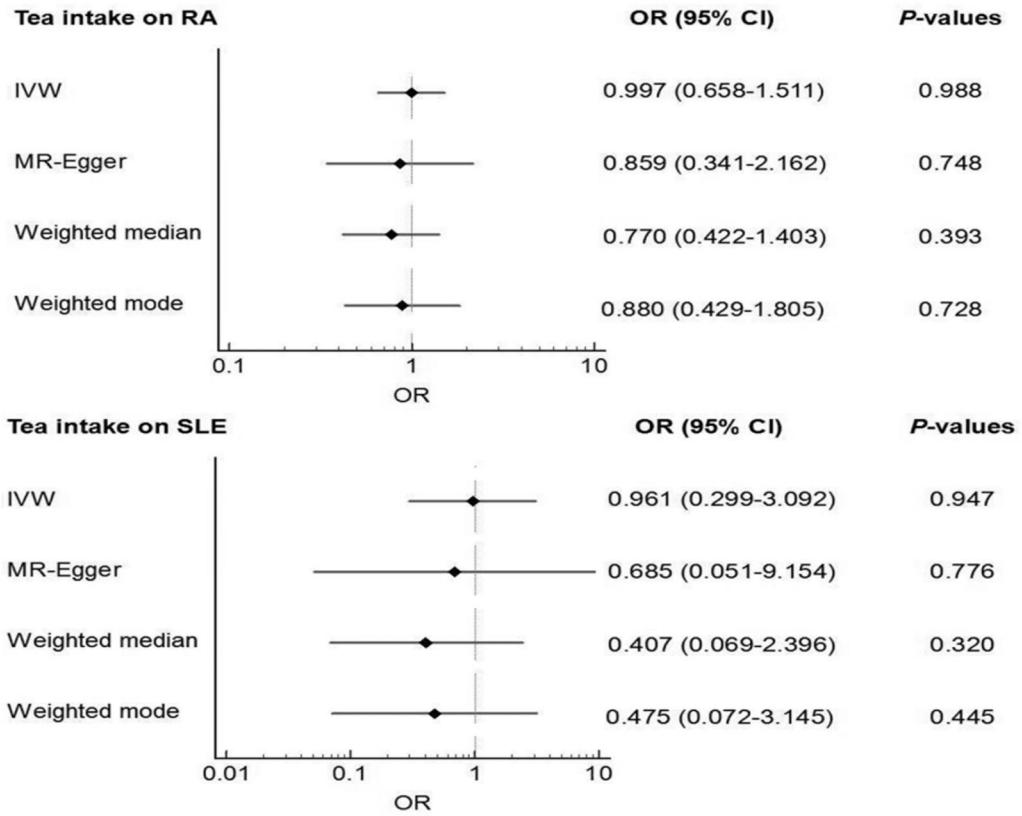


**Fig. 1** Univariable Mendelian randomization analyses for the association of genetically instrumented tea intake with RA and SLE. CI, confidence interval; IVW, inverse-variance weighted; OR, odds ratio; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

test 0.122; tea intake and SLE: *P*-value global test 0.44). The leave-one-out analyses did not identify any outliers for all estimates (Additional file 6: Table S5), indicating that the MR results were not driven by any single SNP. Additional file 7: Table S6 shows the inverse-variance weighted MR results of the causal effect of genetically predicted current tobacco smoking, alcoholic drinks per week, and coffee intake on RA and SLE.

We further carried out a multivariable MR to evaluate the causal effect of tea intake on RA and SLE by adjusting for current tobacco smoking, alcoholic drinks per week, and coffee intake. The results did not suggest any causal association of tea intake with RA after adjusting for current tobacco smoking (OR = 0.992, 95% CI 0.676–1.459, $P = 0.968$), alcoholic drinks per week (OR = 1.046, 95% CI 0.680–1.613, $P = 0.837$), and coffee intake (OR = 0.980, 95% CI 0.660–1.191, $P = 0.902$) (Fig. 2). Similarly, there was no causal association between tea intake and SLE after adjusting for current tobacco smoking (OR = 1.097, 95% CI 0.343–3.521, $P = 0.876$), alcoholic drinks per week (OR = 1.173, 95% CI 0.391–3.525, $P = 0.774$), and coffee intake (OR = 1.246, 95% CI 0.347–4.436, $P = 0.738$) (Fig. 2).

In summary, the main MR analyses using the inverse-variance weighted method and sensitivity analyses using several other reliable MR methods, leave-one-out analyses, and multivariable MR provided consistent results, suggesting that genetically predicted tea intake was not causally associated with RA and SLE.

## Discussion

Tea intake is among the most widely consumed beverages in the world. Our study estimated the causal association of tea intake with RA and SLE in individuals of European ancestry. Across the primary and all sensitivity MR estimates, our study provided no support for a causal effect of tea intake on the risk of RA and SLE.

Tea and its extract such as caffeine and polyphenols have been showed to display antiinflammatory, immunosuppressive, and antioxidative properties. Although tea or its extract was reported to ameliorate animal models of RA and SLE in some experimental studies, observational clinical studies failed to replicate animal findings in humans [14, 16, 36]. Several studies even observed that tea intake was associated with increased risk of RA and SLE [15, 18, 37]. Observational studies are susceptible to

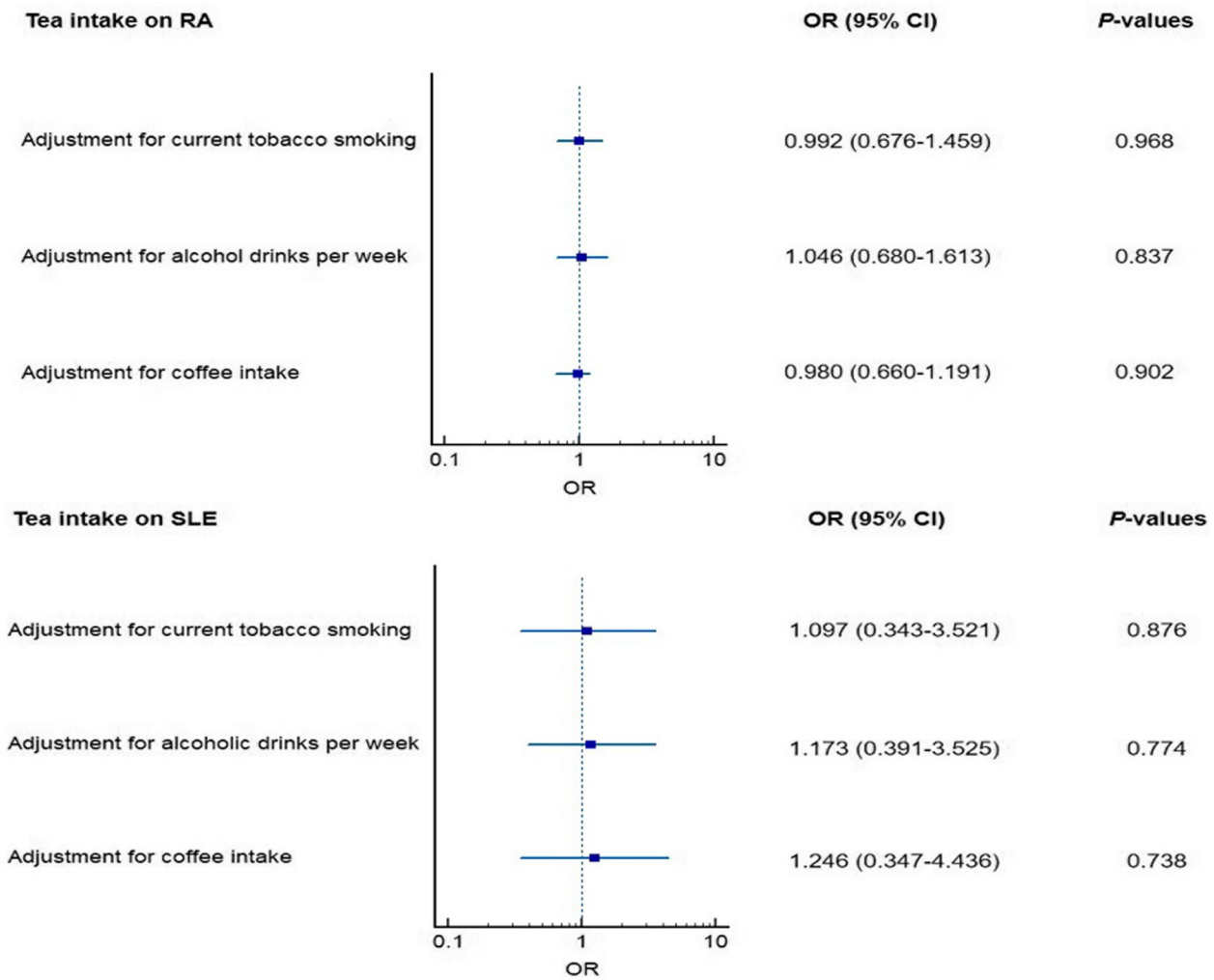


**Fig. 2** Multivariable Mendelian randomization analyses for the association of genetically instrumented tea intake with RA and SLE. CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

biases such as residual confounding and selection bias [38]. It is possible that the prior observational studies may not reliably control for these biases. In some case–control studies, control subjects were not selected for matching RA or SLE patients on confounding factors. For example, the study by Kiyohara et al. [15] recruited university students and staffs from nursing homes and clinics as control subjects; they had different characteristics compared with SLE patients. In addition, some observational studies collected information on tea intake and confounding factors only at baseline, which may lead to misclassification. Furthermore, tea is frequently consumed in combination with cigarettes and alcohol. It is thought that conventional observational studies have difficulty in separating the effect of tea from cigarettes and alcohol when evaluating the effect of tea intake on RA and SLE. Besides these shortness, conventional observational studies are not able to determine the causal association of tea intake with the risk of RA and SLE. Therefore, reliable conclusions may not be drew from conventional observational studies.

MR is a promising approach in genetic epidemiology. It can minimize potential biases in conventional observational studies and perform causal inference. To clarify the causal association, we performed a two-sample MR using summary-level statistics from large GWAS datasets. We selected SNPs that were strongly associated with tea intake as instruments; the potential for weak instrument bias was reduced since all instruments had sufficiently large F-statistics (> 10). The main MR analyses using the inverse-variance weighted method showed null causal associations of tea intake with RA and SLE and no evidence of heterogeneity. The sensitivity analyses using the MR-Egger, weighted median, weighted mode, and

multivariable MR analyses yielded completely consistent results with those of the main MR analyses. The MR-Egger intercept test, the MR-PRESSO global test, and the leave-one-out analyses indicated low likelihood of pleiotropy. Thus, our MR findings were robust against violations of the MR assumptions.

These findings are in agreement with two prior meta-analyses evaluating the association between tea and risk of RA [39, 40]. Lee et al. [39] summarized available evidence from three studies (cohort or case–control design) including 638 patients with RA and 113,998 controls. They found no association between tea intake and the incidence of RA in the overall meta-analysis (relative risk (RR) = 0.88, 95% CI = 0.62–1.24, $P = 0.463$) and subgroup analysis according to study design (case–control design: RR = 1.00, 95% CI = 0.58–1.72, $P = 1.000$; cohort design: RR = 0.68, 95% CI = 0.27–1.71, $P = 0.410$). Similarly, the meta-analysis by Asoudeh et al. [40] using prospective cohort studies (823 RA cases and 191,313 controls) did not observe significant relation between tea consumption and the risk of RA (RR = 1.05, 95% CI 0.73–1.53). There were no meta-analyses estimating the relationship between tea and SLE risk. Our findings were also in line with a recently published MR study by Chen and colleagues who showed no effect of tea consumption on RA (sample size: 58,284, OR = 1.24, 95% CI 0.81–1.91) [41]. Compared with that MR study, we increased the statistical power by using a much larger study sample (447,485 participants). Additionally, we controlled for several confounding lifestyle factors including smoking, alcohol drinking, and coffee consumption using multivariable MR, which was important but neglected by Chen and coworkers [41].

This MR study is subject to some limitations. Firstly, we assessed the effects of black tea and green tea together but did not separate their effects, due to the questionnaire design in the original GWAS study. Black tea and green tea differ in terms of chemical composition [41]. The major polyphenolic compounds of black tea include thearubigins and theaflavins, whereas green tea is rich in catechins such as epicatechin-3-gallate and epicatechin and EGCG [42]. Limited evidence showed that consumption of black tea and green tea exhibited a different association with SLE risk [15]. We hope that future MR studies can evaluate the causal effect of black tea and green tea intake on RA and SLE separately when more data becomes available. Secondly, we were not able to assess non-linear associations since two-sample MR can only assess linear associations. Future MR analyses are needed to evaluate the non-linear relationships of tea intake with RA and SLE. Thirdly, it is known that one of the shortcomings of MR is limited statistical power. We cannot rule out completely the possibility that the null association of tea intake with RA and SLE was owing to a small causal role which was undetectable in this MR analysis. However, it is certain that our MR results did not suffer from weak instrument bias since the instruments used were strong (F-statistic > 10). Fourthly, since different ethnic populations such as Europeans and Asians have different tea intake habits, more research is required to investigate the generalizability of our results to races other than Europeans.

## Conclusion

In sum, we did not find any effect of genetically predicted tea intake on the risk of RA and SLE based on summary-level data from large GWAS in individuals of European ancestry.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42358-023-00290-7.

**Additional file 1: Table S1.** Summary results of the SNPs associated with tea intake.

**Additional file 2: Table S2.** Summary results of the SNPs associated with current tobacco smoking.

**Additional file 3: Table S3.** Summary results of the SNPs associated with alcoholic drinks per week.

**Additional file 4: Table S4.** Summary results of the SNPs associated with coffee intake.

**Additional file 5: Figure S1**. Schematic representation of the Mendelian randomisation design. Our Mendelian randomization study is based on three key assumptions: (1) instruments are associated with tea intake; (2) instruments have no associations with confounding factors; and (3) instruments directly affect rheumatoid arthritis and systemic lupus erythematosus through tea intake.

**Additional file 6: Table S5**. Leave-one-out analyses using the IVW method.

**Additional file 7: Table S6.** The IVW MR estimates on the causal effect of genetically predicted current tobacco smoking, alcoholic drinks per week, and coffee intake on rheumatoid arthritis and systemic lupus erythematosus.

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**Author contributions**
JH, conceptualization; JH, methodology; RBL and JH, resources; RBL and JH, validation and formal analysis; RBL and JH, writing-original draft preparation; JH, supervision; JH, writing-review and editing. Both authors read and approved the final manuscript.

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**Availability of data and materials**
This Mendelian randomization study is based on summary-level data that have been made publicly available in the IEU GWAS database (https://gwas.mrcieu.ac.uk/).

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors have no competing interests to declare.

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## Publisher's Note