The impact of tea consumption on the risk of depression: A Mendelian randomization and Bayesian weighting algorithm study

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ABSTRACT

Background and Objectives: The precise impact of tea consumption on the risk of depression remains unclear. This study aimed to explore the relationship between the consumption patterns of tea and the likelihood of depression onset, utilizing a two-sample Mendelian randomization (MR) methodology. **Methods and Study Design:** We utilized available genome-wide association study (GWAS) datasets on tea intake and depressive disorders. To investigate the causal relationship between tea consumption and depression, we employed a set of two-sample Mendelian Randomization (MR) methods. These included the inverse-variance weighted (IVW) analysis, weighted median approach, and MR-Egger regression. Additionally, we utilized MR-PRESSO and the MR-Egger intercept test for the detection of pleiotropic effects. To ensure the robustness and consistency of our findings, a sensitivity analysis was carried out, applying the 'leave-one-out' strategy. The Bayesian weighted Mendelian randomization (BWMR) was employed to conduct additional testing on the obtained results. **Results:** The study's outcomes revealed a causal association between elevated tea intake and an increased risk of depression (Inverse-Variance Weighted Analysis: Odds Ratio [OR] = 1.029, 95% Confidence Interval [CI]: 1.003–1.055, p = 0.027). This was observed despite variations in instrumental variables and the nonexistence of horizontal pleiotropy. Further, the robustness of our Mendelian Randomization investigation was affirmed through the implementation of the 'leave-one-out' method in our sensitivity analysis. The findings from BWMR were in line with those obtained from IVW (BWMR: OR=1.030, 95% CI: 1.003–1.057, p = 0.029). **Conclusions:** The results from this study indicate a substantial and positive causal link between the regularity of tea drinking and the risk of depression onset.

Key Words: tea consumption, depression, Mendelian randomization, causal association

INTRODUCTION

Depression is a widely observed psychological condition, marked by experiences of persistent low spirits, a diminished interest or enjoyment in activities, known as anhedonia, coupled with a condition of acquired helplessness. It is the psychiatric condition with the highest suicide rate. World Health Organization data indicates that around 280 million individuals globally experience various levels of depression. The number of patients is continuously increasing, and the onset age is trending younger.[1] Currently, treatment options for depression are very limited. Diet, exercise, and other modifiable risk factors are considered potential

effective strategies for intervening in depression. As the second most popular drink in the world following water, tea has gained interest for its possible health benefits.[2] Nevertheless, the relationship between tea drinking and depressive symptoms is not well-defined. Evaluation of aggregated data from various observational studies suggests a reverse correlation between the regular consumption of tea and the probability of encountering depression.[3] It has been reported that compounds in tea, such as teasaponin, may exert protective effects against depression by upregulating the extracellular regulated protein kinases(ERK)/yclic AMP response element binding protein (CREB)/brain-derived neurotrophic factor (BDNF) signaling pathway.[4] However, the link between drinking tea and depression is still not definitive. Research focusing on caffeine, another key ingredient in tea, suggests that consuming caffeine might elevate the likelihood of experiencing depression and anxiety, particularly among college students.[5] Consequently, the role of tea consumption in potentially slowing the progression of depression remains inconclusive. Moreover, observational studies can be affected by possible confounding variables, the issue of reverse causality, and the limitations of smaller sample sizes.

Taking these elements into account, our study employed a bi-sample Mendelian randomization (MR) approach to investigate the causal link between tea consumption and the incidence of depression. This MR methodology leverages single nucleotide polymorphisms (SNPs) as genetic proxies to assess the effect of a specific exposure on a resultant condition, addressing the constraints inherent in observational studies.[6] The conventional methods for MR analysis also face the challenge of assessing the impact of weak effect and weak level pleiotropy on the findings. Therefore, to further validate the reliability of our results, we employed a novel verification approach known as The Bayesian weighted Mendelian randomization (BWMR).[7] Consequently, our research findings pointed towards a causal relationship between the quantity of tea consumed and an increased risk of depression.

MATERIALS AND METHODS

Data sources

Relevant Genome-Wide Association Study(GWAS) datasets were sourced from the online repository (https://gwas.mrcieu.ac.uk). Specifically, the dataset for tea consumption (Identifier: ukb-b-6066) was obtained from a GWAS that involved 447,485 individuals of European descent. The GWAS dataset for depression (ID: ebi-a-GCST005902) came from another GWAS analysis, comprising 322,580 participants of European ancestry (Supplementary Table 1).

Selection of instrumental variables

MR analysis uses SNPs as instrumental variables (IVs) in examining the causative link between an exposure and its outcome. Initially, adhering to the primary Mendelian randomization prerequisite that SNPs should have a strong correlation with the exposure factor, we chose SNPs that demonstrated a significant association at the genome-wide significance level (*p*-value less than 5×10^6).[8] Secondly, we established criteria to guarantee the independence of instrumental variables representing exposure. This involved setting a linkage disequilibrium (LD) threshold with an r^2 value below 0.001 and a genetic distance of 10,000 kilobases. Thirdly, in order to synchronize the datasets for both the exposure and outcome variables, we utilized the frequencies of effect alleles, concurrently excluding palindromic SNPs that displayed intermediate allele frequencies. Lastly, adhering to the MR's second principle that genetic variants should be independent of potential confounders, we referenced the PhenoScanner V2 database to exclude SNPs associated with confounding elements like schizophrenia,[9] obesity,[10] alcoholism,[11] diabetes,[12] anxiety,[13] smoking,[14] and loneliness[15] were excluded. Moreover, we evaluated the potential for weak instrumental variable bias within the selected instrumental variables. This was accomplished by calculating the F-statistic; a F value greater than 10 suggests the absence of weak instrumental variable bias, thereby reinforcing the validity of the assumed association.

Application of Mendelian randomization analysis

In our research, we utilized a bi-sample MR approach, incorporating a range of techniques such as IVW analysis, weighted median, MR-Egger regression, simple mode, and weighted mode, to deduce causal relationships. The primary method in our MR analysis was IVW. This technique integrates the MR estimates from each SNP to provide a comprehensive, weighted assessment of potential causal influences. The credibility of IVW analysis findings is highest when there is no evidence of horizontal pleiotropy in the instrumental variables.[16]

Cochran's Q test was applied in our study to evaluate the heterogeneity present in the SNPs.[17] If no significant heterogeneity is observed (*p*-value is greater than 0.05), a fixed-effect model is used; otherwise, a random-effect model is employed. To evaluate pleiotropy, several techniques were employed: firstly, the MR-Egger intercept was utilized to identify directional pleiotropy;[18] secondly, the Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) approach was used for the assessment and adjustment of horizontal pleiotropy.[19] Furthermore, a 'leave-one-out' sensitivity analysis was carried out to ascertain the impact of single SNPs on the causality.

BWMR verification

The BWMR method effectively enables the investigation of causal relationships between exposure and outcomes, while also evaluating the impact of uncertainty arising from weak effect and weak level pleiotropy through standard error and P-value analysis based on GWAS summary statistics.[7] Therefore, it is imperative to further validate the findings obtained from MR Analysis.Therefore, we employ BWMR to further validate the reliability of IVW (p <0.05).

Statistical analysis

We executed all statistical evaluations using R software (version 4.2.1), specifically employing the 'Mendelian Randomization' (version 0.4.3) and 'Two Sample MR' (version 0.5.6) packages for analysis. For our analysis, a p-value less than 0.05 in a two-tailed test was considered to denote statistical significance.

RESULTS

Selection of instrumental variables (IVs)

"Following the exclusion of IVs affected by linkage disequilibrium, our study incorporated 143 SNPs that met the criteria (p-value less than 5 x 10^6, R-squared less than 0.01) as depicted in Figure 2. The PhenoScanner database was utilized to evaluate the linkage between SNPs and possible confounding elements. "Ultimately, 23 SNPs were omitted from the analysis because they were linked to potential risk determinants for depression. Specifically, rs80318442 and rs62092408 were excluded due to their association with schizophrenia; rs1394094, rs1481012, rs4410790, rs12765951, rs12295734, rs6265, rs2472297, rs9302428, rs1428831, rs1285244, rs11878917, and rs2318540 due to obesity; rs713598 due to alcohol consumption; rs2497304, rs1275193, and rs9937354 due to diabetes; rs35596618, rs73187605, and rs2403304 due to anxiety; rs1453548 due to smoking; and rs72797284 due to loneliness. The residual 120 SNPs, each having an F-value exceeding the standard threshold of 10, were chosen as instrumental variables for assessing tea consumption, suggesting the absence of bias due to weak instruments.

MR analysis results

MR-Egger regression results showed Cochran's Q = 198.38, Q_df = 113, p = 0.000; IVW results showed Cochran's Q = 204.28, Q_df = 114, p = 0.000, indicating some heterogeneity

among SNPs (Figure 3A, Supplementary Table 2）. As a result, a random-effects model was selected to reduce the influence of heterogeneity. The intercept of the MR-Egger regression was close to zero (b= 0.001, p = 0.070), suggesting the absence of horizontal pleiotropy (see Supplementary Table 3). Additionally, the MR-PRESSO tests revealed no anomalous outliers. Considering the lack of horizontal pleiotropy in the instrumental variables, the Inverse-Variance Weighted (IVW) approach was predominantly employed in our Mendelian Randomization (MR) study. Our findings revealed a causative link between increased tea consumption and a higher depression risk (OR = 1.029, 95% CI: 1.003–1.055, p = 0.027), as illustrated in Figure 3B (Scatter Plot) and 3C (Forest Plot). Further details can be found in Supplementary Table 4.

A leave-one-out sensitivity analysis was conducted to verify the stability and reliability of these results. This process entailed systematically omitting each SNP in sequence and subsequently assessing the influence of the residual SNPs on the aggregate Mendelian Randomization outcomes. This was done to ascertain if any single instrumental variable was disproportionately influencing the causal association. The outcomes of this sensitivity analysis, depicted in Figure 3D, affirmed the reliability of our MR analysis results.

The results of BWMR analysis and verification

The BWMR method was employed to further examine the reliability of IVW analysis findings. The outcomes revealed that BWMR provided support for a causal association between tea consumption and an elevated risk of depression (OR=1.030, 95% CI: 1.003-1.057, p =0.029). Further details can be found in Supplementary Table 5.

DISCUSSION

Depression is a common multifactorial neuropsychiatric disorder. Current antidepressant treatments have limitations, such as suboptimal efficacy, prolonged treatment duration with the possibility of relapse, and severe side effects.20 Nearly half of clinical trials have shown a minimal difference in the Hamilton Depression Rating Scale scores between the medication and placebo groups.[21] Moreover, significant side effects like dizziness, cognitive impairment, and arrhythmias have been reported with the clinical use of antidepressants.[22-24] Therefore, exploring non-pharmacological factors like natural dietary supplements and exercise as interventions for depression is of great importance. Tea, with its potent antioxidant activity, is used worldwide as a popular herbal beverage. It has garnered attention in recent years for its

potential role in the treatment of depression. However, studies involving tea interventions for depression and depressive symptoms are mostly clinical observational studies, inherently limited in their research scope.

Hence, the primary objective of this research is to elucidate the causative link between the intake of tea and the occurrence of depression, providing reference for non-pharmacological treatment of depression.

In our study, we utilized publicly available GWAS data and employed a bi-sample MR approach to investigate the causal link between tea consumption frequency and the probability of depression onset. The results of our research indicate a direct causal relationship between frequent tea consumption and a heightened risk of depression.

Earlier research has proposed that tea consumption may contribute to mitigating symptoms of depression. A comprehensive examination and meta-analysis of diverse observational studies have pointed out that certain types of tea, along with caffeine intake, might lower the risk of developing depression.[25] In a similar vein, another meta-analysis focusing on randomized controlled trials (RCTs) identified a notable link between the intake of both tea and coffee and a diminished risk of depression among various populations.[26]

It is believed that tea contains phytochemicals and antioxidants such as catechins, chlorogenic acids, and cucurbitacins, which can promote dopamine release, thereby alleviating depression.[27] Nonetheless, the effect of tea drinking on depressive states continues to be a subject of debate. A cohort study encompassing 2,232 middle-aged men in Eastern Finland found no substantial association between tea and caffeine consumption and depression.[28] Additionally, a prospective cohort analysis of individuals in the UK Biobank identified a notable positive relationship between the intake of free sugars during tea consumption and the risk of depression.[29] The risk of depression and anxiety symptoms may also be attributed to caffeine, a component of tea.[5] From a genetic perspective, our study supports this view. The suggested protective impact of tea drinking on depression in prior research may be skewed due to unaccounted confounding variables. There is also a possibility that the protective effects of tea on depression might be partly explained by the social interactions during tea-drinking, rather than tea consumption itself.[30]

Though theories have been suggested regarding how tea consumption might impact depression risk, the direct cause-and-effect relationship is still not fully understood. MR analysis reduces potential biases common in observational studies, such as residual confounding or reverse causality. This study constitutes the initial comprehensive investigation into the causal relationship between tea consumption and depression risk

employing MR techniques. The results of our research indicate a positive correlation between the regularity of tea drinking and the risk of developing depression (IVW: OR=1.029, CI:1.003-1.055, p =0.027). Nonetheless, the results of MR analyses are often prone to the influence of pleiotropy.31 In response to this issue, the MR-PRESSO test was employed in our analysis. The outcome of this test, with a p-value > 0.05, indicated that the impact of genetic pleiotropy on our findings could be disregarded. BWMR represents a statistical technique for causal inference that diverges from conventional MR Analysis. The latter method is characterized by certain constraints, such as disregarding the impact of multiple weak SNPs on exposure effects and the potential for selection bias in SNP exposure effects. BWMR incorporates a unified statistical framework that addresses the uncertainties and biases associated with weak effects estimated in Genome-Wide Association Studies (GWAS) within the context of two-sample MR analysis. The above MR Findings are also supported by BWMR simultaneously (OR=1.030, CI: 1.003–1.057, p =0.029).

One of the constraints of this research lies in its use of GWAS data solely from European populations. As a result, the applicability of our results to different demographic groups necessitates additional examination. Secondly, the inclusion of a large number of SNPs resulted in some heterogeneity in the analysis results. However, these are strong instrumental variables, and no horizontal pleiotropy was found, which does not affect the outcomes of our study. Lastly, in our research, tea consumption was considered as a whole, without categorizing based on the type of tea, preparation methods, or brewing techniques. This aspect necessitates more comprehensive and extensive research in the future.

Conclusion

In summary, our research utilized a bi-sample MR methodology to uncover a causal link between the consumption of tea and the likelihood of experiencing depression. The outcomes of our research indicate a direct and positive relationship between the amount of tea consumed and the increased probability of experiencing depression. Our findings provide further insights into the genetic research on dietary factors intervening in depression and do not recommend daily tea consumption as an advisory intervention for depression.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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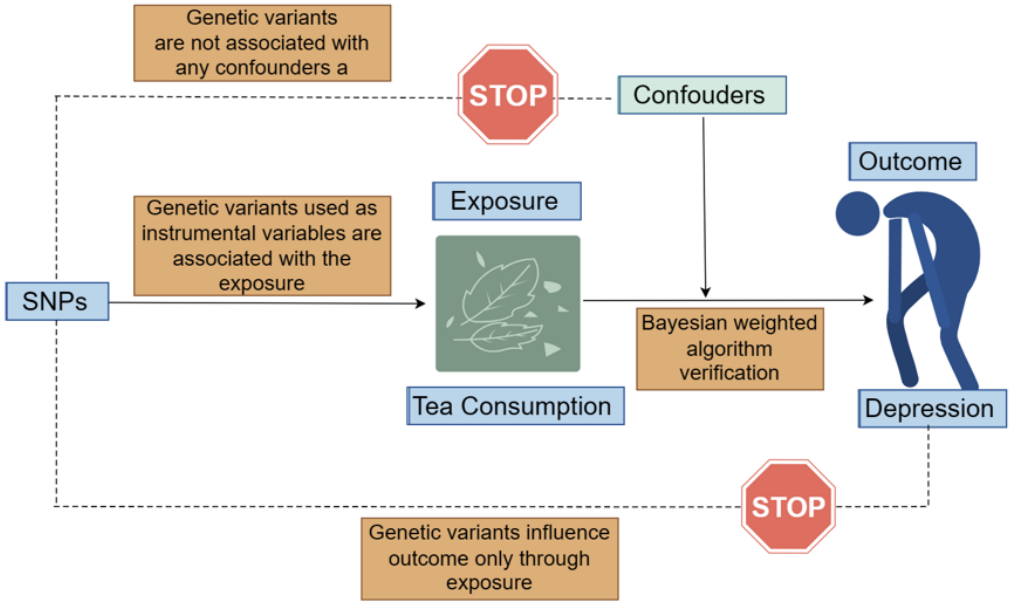

Figure 1. Graphical abstract.

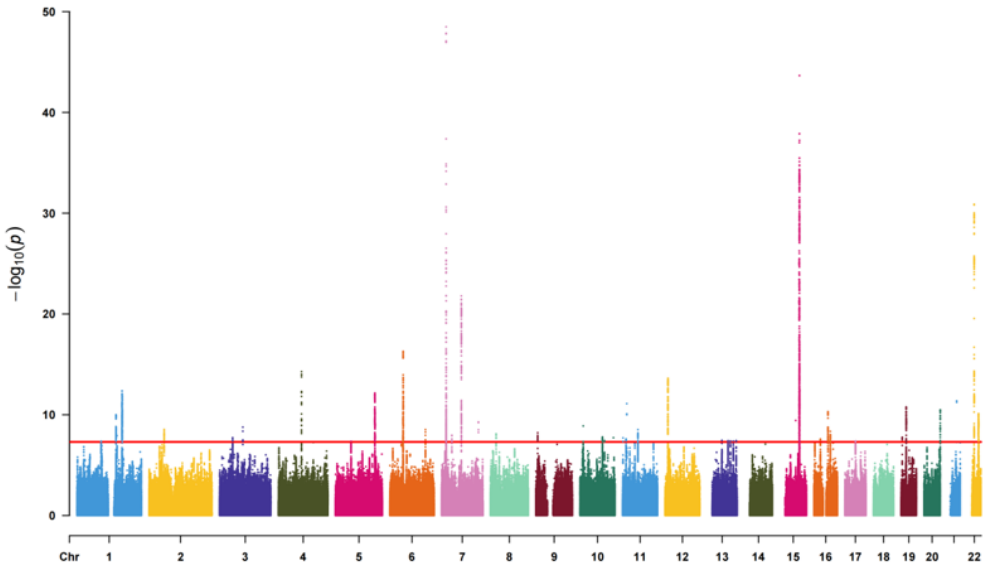

Figure 2. The outcome of IVs selection.

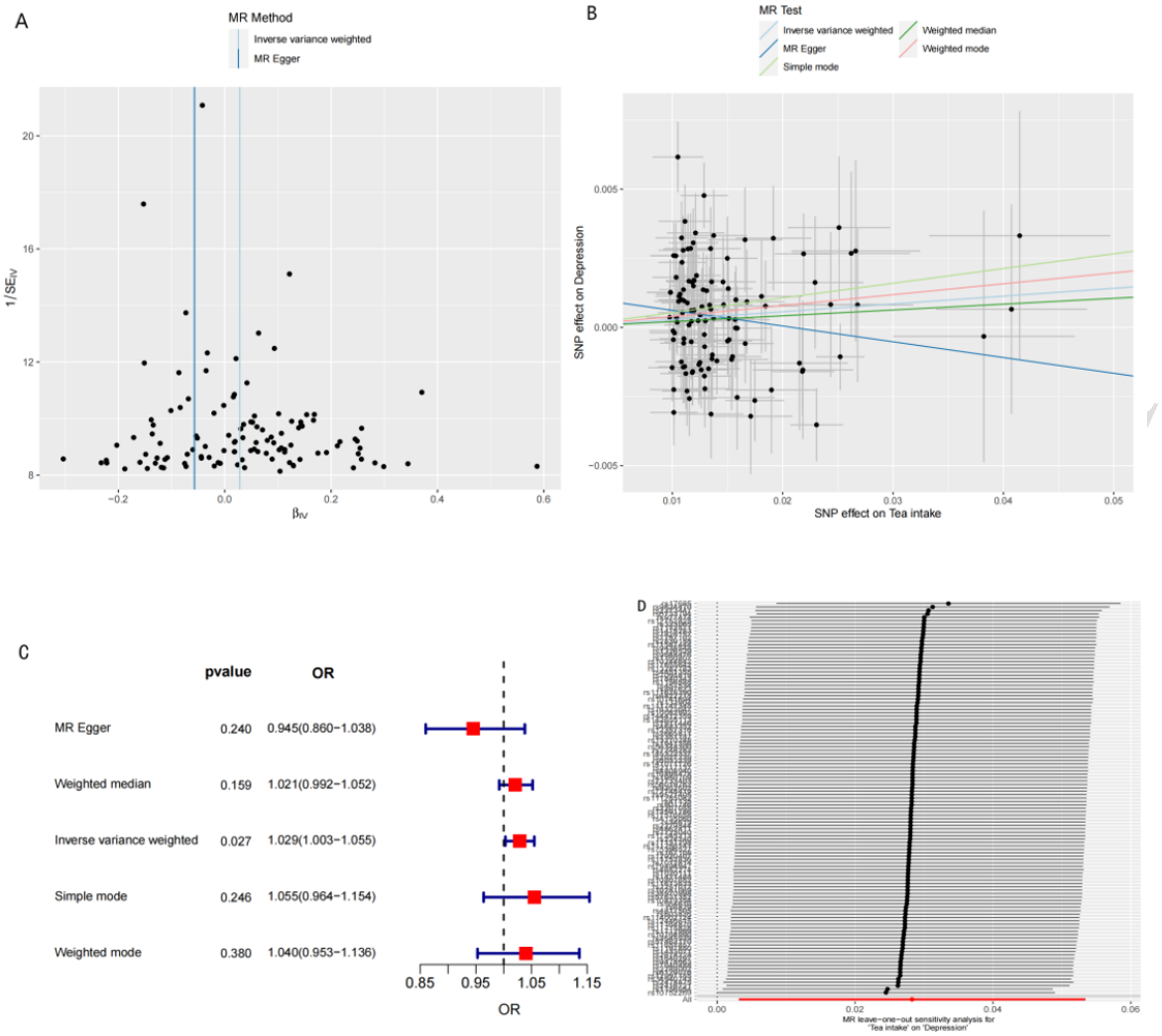

Figure 3. Mendelian randomization analysis. (A) Funnel plot analysis of the causal association between tea consumption and the risk of depression in a meta-analysis study. (B) MR Scatter plot analysis of causal relationship between tea intake and risk of depression. (C) Forest map of MR Analysis of causal relationship between tea intake and depression risk. (D) Graph of sensitivity analysis result of "leave one method".

Supplementary Tables

Supplementary Table 1. The present study utilized the GWAS summary data to provide comprehensive details

Name	GWAS ID	Sample size	Number of SNP	Gender	Population	Year
Tea intake	ukb-b-6066	447485	9,851,867	Male/Female	European	2018
Depression	ebi-a-GCST005902	322,580	7,624,934	Male/Female	European	2018

Supplementary Table 2. Heterogeneity test results

Outcome	Exposure	Q	Q_df	Q_P
Depression	Tea intake	198.382	113	0.000
Depression	Tea intake	204.275	114	0.000

Supplementary Table 3. MR-Egger pleiotropy test results

Outcome	Exposure	Egger_intercept	SE	*p*
Depression	Tea intake	0.001	0.001	0.070

MR: Mendelian randomization; SE: standard error.

Supplementary Table 4. MR analysis results

Method	Number of SNPs	Beta	SE	*p*
MR Egger	115	-0.057	0.048	0.240
Weighted median	115	0.021	0.015	0.171
Inverse variance weighted	115	0.028	0.013	0.027
Simple mode	115	0.053	0.047	0.259
Weighted mode	115	0.039	0.044	0.370

IVW: inverse-variance weighted method; MR: Mendelian randomization; WM: weighted median method; SNP: single nucleotide polymorphism; SE: standard error

Supplementary Table 5. BWMR analysis results

Method	OR	Beta	*P*
BWMR	1.030 (1.003-1.057)	0.029	0.029

BWMR: Bayesian Weighted Mendelian Randomization; OR: Odds Ratio.