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A Mendelian randomization study reveals a causal relationship between tea consumption and esophageal cancer

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Abstract. This study aims to evaluate the causal relationship between tea consumption and esophageal cancer using a bidirectional Mendelian Randomization (MR) approach. Methodologically, genetic instruments for tea intake were derived from a Genome-Wide Association Study (GWAS) involving 447,485 participants in the UK Biobank. Thirty-nine tea-associated Single Nucleotide Polymorphisms (SNPs) were selected and analyzed using two-sample MR to examine causality. The esophageal cancer data were obtained from the NA consortium's publicly available GWAS, which includes 998 cases and 475,308 controls. A reverse MR analysis was also conducted to explore potential reverse causality. The results demonstrate a causal link between tea consumption and esophageal cancer. Specifically, using the inverse-variance weighted (IVW) method, a one standard deviation increase in tea intake was associated with a 194.5% increase in esophageal cancer risk (OR = 2.945, 95% CI: 1.794–4.833). Similar results were observed using the weighted mode (OR = 5.590, 95% CI: 2.713–11.519) and weighted median (OR = 4.446, 95% CI: 2.260–8.748) methods. The IVW method again showed a consistent result (OR = 2.945, 95% CI: 1.551–5.592). However, there was no evidence supporting reverse causality (IVW: $P > 0.05$). Overall, genetic evidence from bidirectional MR analyses indicates that increased tea consumption raises the risk of esophageal cancer, although no reverse causal relationship was found.

Keywords: tea consumption, esophageal cancer, mendelian randomization, causality, genetic epidemiology

1. Introduction

Esophageal Cancer (EC) is the ninth most common cancer globally and the sixth leading cause of cancer-related mortality [1]. It is a severe malignancy in terms of both mortality and prognosis, with approximately 500,000 new cases and 400,000 deaths reported annually worldwide. The five-year survival rate for EC is less than 20% [2]. As a growing public health concern, its incidence is projected to increase over the next decade. Squamous cell carcinoma is the most common histological type globally, with particularly high incidence in developing countries. Conversely, in developed countries, the prevalence of Gastroesophageal Reflux Disease (GERD) and obesity has led to a sharp increase in esophageal adenocarcinoma over the past 40 years [3]. In Asia, squamous cell carcinoma remains dominant, whereas adenocarcinoma is becoming more common in Western countries [4]. Known risk factors include smoking, alcohol consumption, nutritional deficiencies (such as vitamins and minerals), chronic esophagitis, obesity, and GERD. Genetic, environmental, and lifestyle factors also contribute to EC risk [5]. Primary prevention strategies, such as dietary and lifestyle modifications, can help reduce the incidence of EC [6].

Tea is widely consumed around the world. Based on the degree of fermentation, tea is typically categorized into six types: white, green, yellow, oolong, black, and dark tea. It contains various phytochemicals, including polyphenols, pigments, polysaccharides, alkaloids, free amino acids, and saponins. Numerous studies have shown that tea has multiple health benefits, including antioxidant, anti-inflammatory, immunomodulatory, anticancer, cardioprotective, antidiabetic, anti-obesity, and hepatoprotective effects [7]. Existing research on the causal link between tea consumption and esophageal cancer mainly consists of case-control studies. Some findings suggest that tea may have inhibitory effects on the development of certain cancers, particularly esophageal cancer [8]. However, there is insufficient evidence to support a protective effect of tea against lung, esophageal, or gastric cancers [9]. Although Randomized Controlled Trials (RCTs) are ideal for resolving such questions, they are resource-intensive. In recent years, Mendelian Randomization (MR) has become a widely adopted method to estimate causal effects between modifiable exposures and disease traits. MR leverages the principle of Mendel's random assortment and independent segregation of alleles, reducing confounding and reverse causality that often affect observational studies. It is

considered a viable alternative to RCTs. Given the lack of previous MR studies in this area, the present study aims to rigorously evaluate the causal relationship between tea consumption and esophageal cancer through Mendelian Randomization analysis.

2. Materials and methods

2.1. Study design

Mendelian Randomization (MR) is an analytical method that uses genetic variants as instrumental variables (IVs) to assess causality. It relies on three core assumptions: (1) The genetic IVs are strongly associated with the exposure. (2) The genetic IVs are not associated with any confounding factors. (3) The genetic IVs influence the outcome solely through the exposure, and not through alternative pathways (see Figure 1) [10]. This study adopted a two-sample, bidirectional MR design using two large GWAS datasets. All informed consent and ethical approvals were obtained from the original studies.

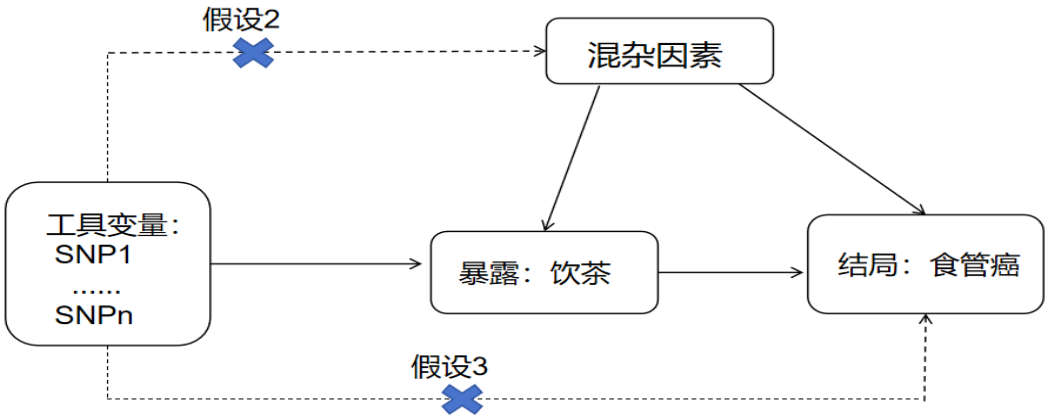


Figure 1. Schematic diagram of Mendelian randomization study design

2.2. Data sources

The GWAS summary statistics for tea consumption were obtained from the UK Biobank (Phenotype Code: 1488_raw), comprising 447,485 individuals of European ancestry. Tea intake data were self-reported via questionnaire, based on the question: "How many cups of tea (including black and green tea) do you drink daily?" The GWAS adjusted for sex, genotyping array, and the top ten principal components. The average tea intake was 3.51 ± 2.85 cups/day. Detailed data are available at https://gwas.mrcieu.ac.uk/ (GWAS ID: ukb-b-6066).

GWAS data for esophageal cancer were also derived from UK Biobank, comprising 998 EC cases and 475,308 controls, all of European ancestry. As the datasets are publicly available, raw data lists are not included.

2.3. Instrumental variable selection and harmonization

From the UK Biobank GWAS (ID: ukb-b-6066), 41 SNPs significantly associated with tea consumption at the genome-wide level ($P < 5\times10^{-8}$) and meeting linkage disequilibrium criteria ($r^2 < 0.001$ within a 10,000 kb window) were initially selected. These SNPs were then extracted from the esophageal cancer GWAS dataset for subsequent analyses. After aligning SNPs by chromosome and position, eight palindromic SNPs with intermediate allele frequencies (rs11164870, rs132904, rs1453548, rs2273447, rs2783129, rs56348300, rs713598, rs9302428) were excluded due to ambiguity. Ultimately, 33 SNPs were retained. To assess instrument strength, the F-statistic was calculated for each SNP, with all exceeding $F > 10$, indicating no weak instrument bias. Details are presented in Table 1.

Table 1. Information on instrumental variables related to tea consumption

SNP	Position	EAF	EA	OA	BETA	$S\bar{x}$	P	N	R2	F
rs34619	5:60465365	0.431	A	G	0.012	0.002	4.30E-08	447485	6.73E-05	30.105
rs17576658	13:100272019	0.247	A	G	-0.013	0.002	4.10E-08	447485	6.76E-05	30.261
rs2279844	17:40819809	0.379	A	G	-0.012	0.002	4.00E-08	447485	6.77E-05	30.283
rs2645929	13:56444529	0.813	G	A	-0.015	0.003	3.50E-08	447485	6.83E-05	30.543
rs6829	13:111531264	0.596	T	C	-0.012	0.002	3.70E-08	447485	6.84E-05	30.598

Table 1. Continued

rs7757102	6:137222671	0.555	G	A	-0.012	0.002	3.10E-08	447485	6.88E-05	30.793
rs17245213	11:1679769	0.208	A	G	-0.015	0.003	2.00E-08	447485	7.07E-05	31.642
rs10764990	10:129152608	0.607	A	G	-0.012	0.002	1.90E-08	447485	7.09E-05	31.725
rs57462170	3:50239803	0.109	A	G	0.019	0.003	1.90E-08	447485	7.11E-05	31.821
rs57631352	19:4338173	0.297	G	A	-0.013	0.002	1.70E-08	447485	7.17E-05	32.078
rs2351187	10:86850616	0.319	A	G	0.013	0.002	1.60E-08	447485	7.23E-05	32.364
rs9648476	7:39293033	0.623	A	G	0.013	0.002	1.10E-08	447485	7.34E-05	32.855
rs13282783	8:22088975	0.286	T	C	-0.014	0.002	7.90E-09	447485	7.53E-05	33.717
rs1156588	2:58515375	0.210	G	A	-0.015	0.003	2.90E-09	447485	7.93E-05	35.471
rs2117137	3:89525505	0.405	G	A	0.013	0.002	1.70E-09	447485	8.14E-05	36.425
rs10752269	10:12692902	0.506	A	G	-0.013	0.002	1.30E-09	447485	8.28E-05	37.073
rs141071726	7:17558580	0.027	A	G	0.041	0.007	2.20E-09	447485	8.63E-05	38.608
rs149805207	6:137095269	0.009	G	A	-0.072	0.013	1.10E-08	447485	8.76E-05	39.205
rs12591786	15:60902512	0.159	T	C	-0.018	0.003	3.70E-10	447485	9.08E-05	40.656
rs11587444	1:150722844	0.393	G	A	0.014	0.002	1.00E-10	447485	9.40E-05	42.063
rs9937354	16:53799847	0.424	A	G	-0.014	0.002	4.90E-11	447485	9.70E-05	43.413
rs4808193	19:19410622	0.335	C	T	0.015	0.002	1.70E-11	447485	0.00010	45.576
rs10741694	11:16286183	0.628	C	T	0.015	0.002	7.90E-12	447485	0.00011	47.075
rs4817505	21:34343828	0.390	C	T	0.015	0.002	4.20E-12	447485	0.00011	48.345
rs72797284	5:152031650	0.271	G	A	-0.017	0.002	7.00E-13	447485	0.00012	51.771
rs56188862	1:174189269	0.387	C	T	-0.016	0.002	4.30E-13	447485	0.00012	52.742
rs977474	12:11284772	0.834	T	C	0.022	0.003	2.40E-14	447485	0.00013	58.862
rs1481012	4:89039082	0.112	G	A	-0.026	0.003	5.30E-15	447485	0.00014	61.411
rs2478875	6:51283110	0.209	G	A	0.022	0.003	5.10E-17	447485	0.00016	70.874
rs17685	7:75616105	0.278	A	G	0.023	0.002	1.60E-22	447485	0.00021	95.485
rs9624470	22:24820268	0.580	A	G	0.025	0.002	1.30E-31	447485	0.00031	138.563
rs4410790	7:17284577	0.631	C	T	0.041	0.002	3.40E-76	447485	0.00077	342.831
rs2472297	15:75027880	0.262	T	C	0.053	0.002	2.30E-109	447485	0.00110	493.046

Note: SNP ID denotes single nucleotide polymorphism; EA = effect allele; OA = other (non-effect) allele; $S\bar{x}$ = standard error.

2.4. Statistical analysis

2.4.1. Assessing the causal effect of tea consumption on esophageal cancer

After harmonizing the effect alleles for tea consumption and esophageal cancer, several MR methods were applied to estimate causality, including: Inverse-Variance Weighted (IVW); Weighted median; MR-Egger; Weighted mode. Each method relies on different assumptions regarding the validity of instrumental variables. IVW assumes that all IVs are valid and combines individual SNP-specific MR estimates to produce a pooled causal effect, making it the most commonly used approach [11]. The weighted median method yields consistent estimates if at least 50% of the weight comes from valid instruments [12]. MR-Egger allows for directional pleiotropy and adjusts for its bias [13]. The weighted mode approach groups SNPs based on similarity and weights each by the inverse of its variance, enhancing robustness [14].

2.4.2. Sensitivity analyses

To examine heterogeneity and pleiotropy, multiple sensitivity analyses were performed: IVW and MR-Egger regression were used along with Cochran's Q statistic to test for heterogeneity. MR-PRESSO was employed to detect horizontal pleiotropy and potential outliers. To assess assumption violations (assumptions 2 and 3), the MR-Egger intercept was examined. If the intercept is near zero (<0.1) and $P > 0.05$, the results are considered reliable, suggesting no horizontal pleiotropy. The CAUSE method was applied to account for both correlated and uncorrelated pleiotropy. Funnel plots were used for visual assessment of symmetry, indicating absence or presence of pleiotropy. Leave-one-out analyses evaluated the influence of individual SNPs on overall estimates. Power calculations were conducted using the mRn tool (https://shiny.cnsgenomics.com/mRnd/).

2.4.3. Reverse Mendelian randomization analysis

The reverse MR analysis treated esophageal cancer as the exposure and tea consumption as the outcome, using the same procedures described above. All analyses were performed using R version 4.4.1, with a significance threshold of $\alpha = 0.05$.

3. Results

3.1. Causal effect of tea consumption on esophageal cancer

Using 33 SNPs associated with tea consumption, MR analyses were conducted to evaluate its causal effect on esophageal cancer. The results showed statistically significant associations across all methods: Inverse-Variance Weighted (IVW): OR = 2.945, 95% CI: 1.551–5.592. Weighted Mode: OR = 5.590, 95% CI: 2.056–15.201. Weighted Median: OR = 4.446, 95% CI: 1.238–8.621. These findings suggest that increased tea consumption is causally associated with a higher risk of esophageal cancer (see Figure 2 and Table 2). However, heterogeneity was detected through IVW and Cochran's Q tests.

3.2. Sensitivity analyses

In the MR analysis assessing the causal relationship between tea intake and esophageal cancer, the MR-Egger intercept had a P-value greater than 0.05 (P = 0.273), indicating no evidence of horizontal pleiotropy. Additionally, the CAUSE results showed: Variance explained in exposure: 0.0056; Variance explained in outcome: 0.00012; Directionality p-value: 9.53e–207. These results support a positive causal relationship between tea consumption and increased esophageal cancer risk, even after correcting for correlated and uncorrelated pleiotropy. The scatter plot (Figure 2) illustrates the effect size of each SNP on tea consumption and esophageal cancer risk. The funnel plot (Figure 3) shows symmetrical variation in effect sizes around the point estimates, further indicating no substantial pleiotropy. Finally, a leave-one-out sensitivity analysis (Figure 4) confirmed that no single SNP disproportionately influenced the overall association. Taken together, these findings strongly suggest that increased tea consumption is associated with an elevated risk of developing esophageal cancer.

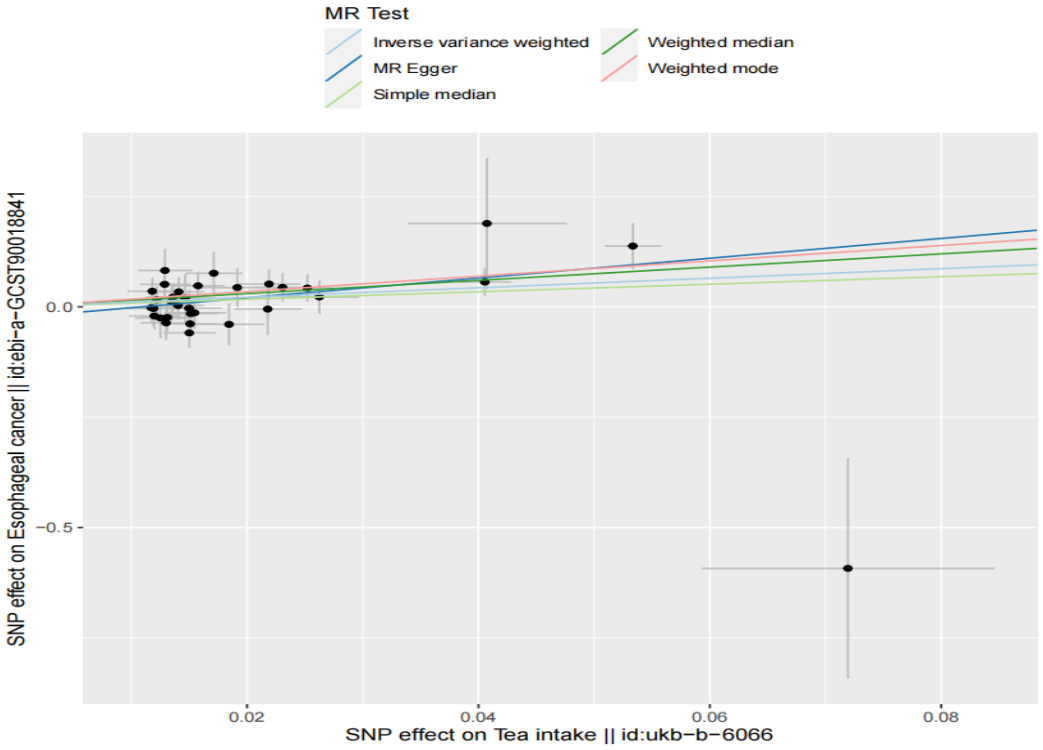


Figure 2. Scatter plot of Mendelian randomization analysis

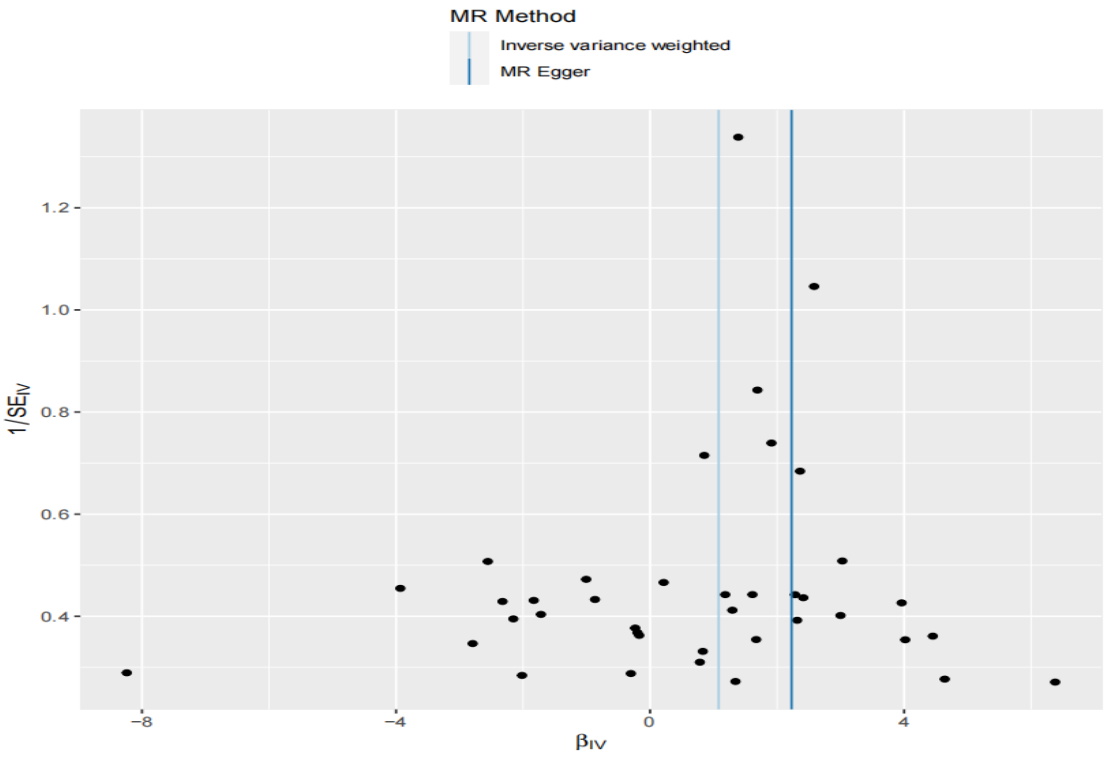


Figure 3. Funnel plot of Mendelian randomization analysis

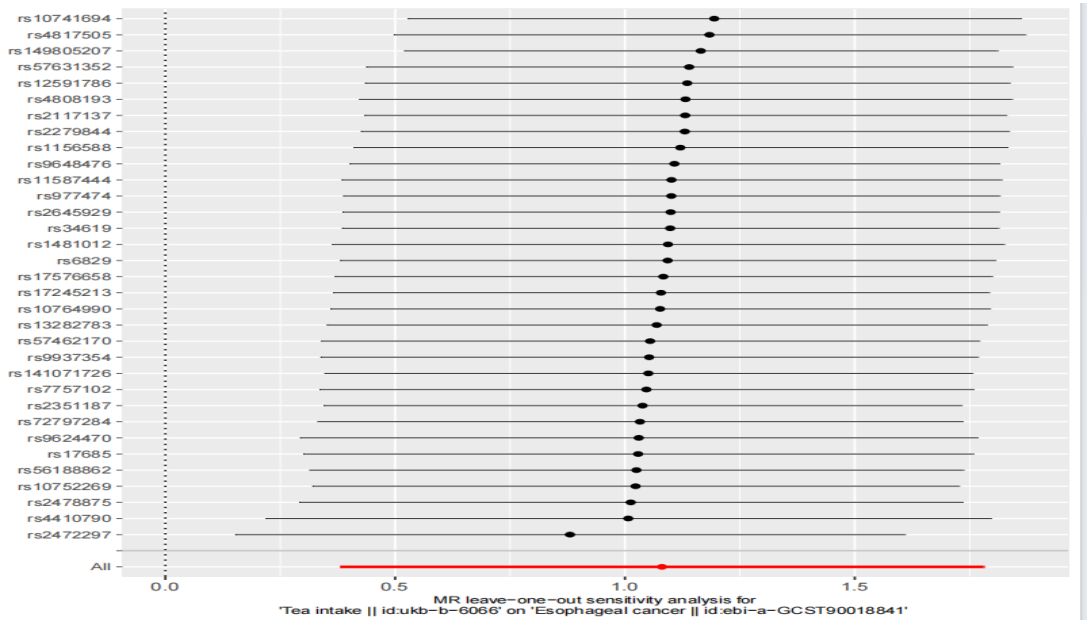
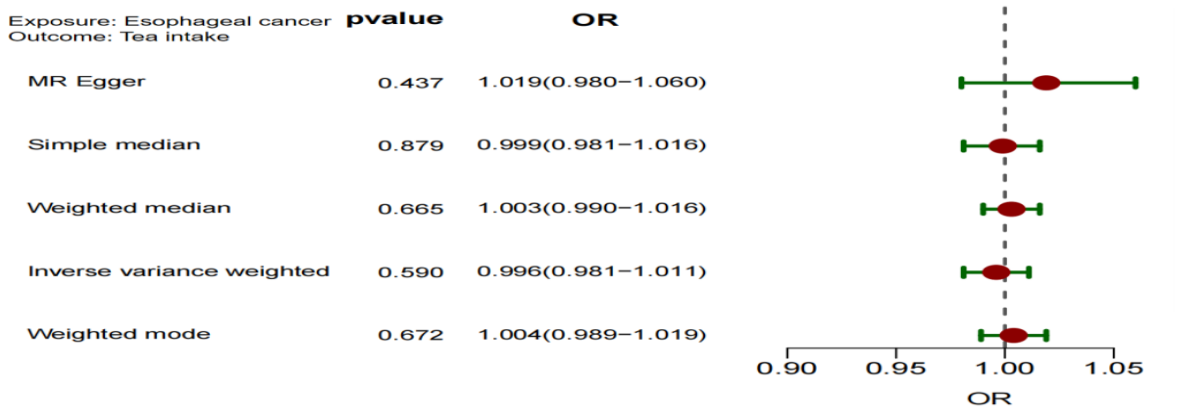


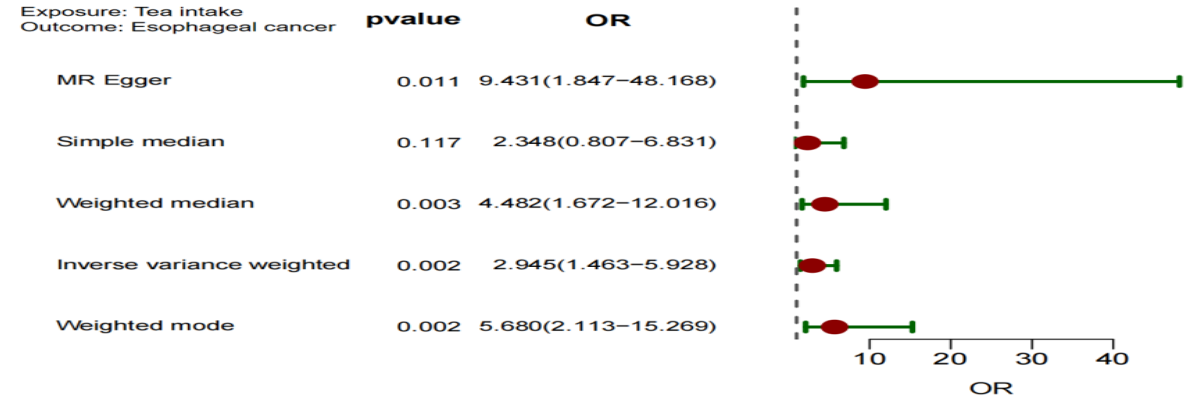
Figure 4. Leave-one-out sensitivity analysis

3.3. Reverse Mendelian randomization analysis

To test for reverse causality, esophageal cancer was treated as the exposure and tea consumption as the outcome. Four SNPs were used in this analysis. The IVW method yielded a non-significant result: P = 0.590. This indicates no evidence of a reverse causal relationship from esophageal cancer to tea consumption (see Figure 5 and Table 2).



(a)



(b)

Figure 5. Forest map

Table 2. Results of Mendelian randomization analysis

Exposure/outcome	IVW		Weighted median		MR Egger		Weighted mode	
	OR(95%CI)	P	OR(95%CI)	P	OR(95%CI)	P	OR(95%CI)	P
Tea intake/esophageal cancer	2.945(1.551~5.592)	0.001	4.446(1.238~8.621)	0.004	9.272(1.992~43.163)	0.005	5.590(2.056~15.201)	0.001
Esophageal cancer/tea intake	0.996(0.981~1.011)	0.590	1.003(0.990~1.016)	0.652	1.019(0.980~1.060)	0.335	1.004(0.989~1.019)	0.634

4. Discussion

This study employed a two-sample, bidirectional Mendelian Randomization (MR) approach to evaluate the causal relationship between tea consumption and the risk of esophageal cancer. The results indicate that increased tea intake causally raises the risk of developing esophageal cancer, while no evidence supports the existence of reverse causality. Numerous observational studies have examined the relationship between tea consumption and esophageal cancer risk, but their findings have been inconsistent. The relationship between tea and cancer risk—particularly esophageal cancer—is complex and multifaceted, as evidenced by the contradictory findings across studies. This paper underscores the value of MR as a method for exploring potential causal links, especially when conventional observational studies are prone to confounding. Although tea has been widely recognized for its antioxidant and anti-inflammatory properties, which are often believed to confer anticancer benefits, the findings of this MR study challenge that assumption. Instead, the results suggest that excessive tea consumption may elevate cancer risk, possibly due to specific tea constituents or the conditions under which tea is consumed. The literature presents a mixed picture of tea's health effects. For instance, a Mendelian Randomization study by Deng et al. found no causal relationship between tea consumption and breast cancer, implying that tea may not significantly affect breast cancer risk [15]. Similarly, research into tea's effects on bone health found no causal association with major skeletal disorders, indicating that tea's health impacts may be context-dependent or

limited [16]. Conversely, Sun et al. emphasized potential adverse effects of tea, linking it to an increased risk of gastroesophageal reflux disease (GERD), a condition known to be a risk factor for esophageal cancer. This indirect association supports the findings of the present study, which suggest that, under certain conditions, high tea consumption may be harmful [17]. On the other hand, Kim and Je offered a broader perspective by reporting that moderate tea consumption was associated with reduced all-cause, cardiovascular, and cancer mortality, indicating a protective effect at lower intake levels [18]. Taken together, the evidence suggests that while moderate tea consumption may have health benefits, excessive intake could pose risks—particularly in relation to esophageal disorders. The inconsistent findings across studies highlight the need for further research that takes into account tea type, preparation methods, and individual genetic variations, to better clarify the role of tea in cancer risk and other health outcomes.

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