Genetic causal relationship between tea intake and cerebral aneurysm: a two-sample Mendelian Randomization Study

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Author contributions

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
CA, cerebral aneurysm; TI, Tea intake; MR, Mendelian Randomization; GWAS, Genome-wide association study; GTI, Green tea intake; HTI, Herbal tea intake; RTI, Rooibos tea intake; IVW, Inverse variance-weighted; UCA, unruptured cerebral aneurysms; EVT, endovascular treatment; NST, neurosurgical treatment; TSMR, Two-Sample Mendelian Randomization; IEU, IEU Open GWAS Project; SNP, Single Nucleotide Polymorphisms; OR, odds ratio; CI, Confidence interval.

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Abstract

Background: Prior research has established a strong link between cerebral aneurysm (CA) occurrence and inflammation. Tea intake (TI) has been found to have anti-inflammatory properties through multiple mechanisms, potentially lowering CA incidence. This study aims to employ Mendelian Randomization (MR) methodology to explore the genetic causality between TI and CA. Methods: We collected Genome-wide association study (GWAS) data for CA, TI, Green tea intake (GTI), Herbal tea intake (HTI), and Rooibos tea intake (RTI). The MR analysis employed the TwoSampleMR package and utilized the inverse variance-weighted (IVW) method. Results: The findings suggest no genetic causal relationship between TI and CA (IVW: OR = 1.10, 95% CI: 0.59–2.05, P = 0.772). Similarly, there is no genetic causal association between GTI and CA (IVW: OR = 1.07, 95% CI: 0.91–1.26, P = 0.388), HTI and CA (IVW: OR = 1.00, 95% CI: 0.89–1.13, P = 0.943), or RTI and CA (IVW: OR = 1.02, 95% CI: 0.96–1.09, P = 0.472). Conclusion: There is no significant causal relationship between TI and CA, and the different types of tea do not change this result. Further MR analysis is needed to investigate whether there is a potential genetic causal association between the quantity of TI and CA.

Keywords: tea intake, cerebral aneurysm, genome-wide association study, Mendelian Randomization Study
Introduction

Cerebral aneurysm (CA) refers to the abnormal dilation of arteries within the brain and affects approximately 3.2% of adults [1]. CA rupture is a serious event that can lead to subarachnoid hemorrhage, causing significant morbidity and mortality [2]. Survival rates after CA rupture are low, with up to 50% of individuals not surviving and many surviving experiencing neurological impairments [3]. Advances in brain imaging have contributed to an increased detection rate of unruptured cerebral aneurysms (UCAs) over time [4]. The prevalence of UCA is estimated to range from 2% to 6% [5]. Treatment options for UCA primarily include open surgery and endovascular interventions [6]. However, these treatments carry the risk of complications. Complication rates for endovascular treatment (EVT) and neurosurgical treatment (NST) are reported at 5.0% and 8.3%, respectively [7]. While EVT has a lower complicate rate than NST, it is associated with higher costs and the possibility of UCA recurrence [8]. Thus, the management of UCA in elderly patients is still a subject of debate [6]. Risk factors for CA rupture currently include aneurysm morphology, smoking history, family history, hypertension, and diabetes [9]. However, research on the risk factors for CA formation is limited, and the underlying factors contributing to CA development remain unclear [10, 11]. Age, gender, genetic factors, hemodynamic changes, hypertension, and smoking are all associated with a higher incidence of new CA cases [12, 13]. The relationship between diet and CA occurrence has received limited research attention. Therefore, it is crucial to identify dietary habits that may be associated with CA development and take preventive measures accordingly.

Tea, the second most consumed beverage globally, contains diverse bioactive compounds [14]. Tea intake (TI) is a significant source of flavonoids for humans, particularly catechin-3-gallate, which has demonstrated preventive and delaying effects on atherosclerosis [15, 16]. TI is regarded as a healthy lifestyle choice, especially in East Asia. Long-term TI has been associated with significant reductions in systolic and diastolic blood pressure [17] and possibly a decreased risk of stroke [18]. The primary components of tea are polyphenols, constituting approximately 15% to 30% of tea leaves [19, 20]. Research suggests that polyphenols show promise in the treatment of abdominal aortic aneurysms [21]. Hence, a potential causal relationship may exist between TI and a lower incidence of CA. However, studies investigating this causal relationship are lacking, leaving the association between TI and CA uncertain. Two-Sample Mendelian Randomization (MR) analysis, an emerging epidemiological research method, employs genetic variation as instrumental variables (IVs) to evaluate the causal effects of exposure factors on outcomes [22]. Due to the unique advantages of IVs, MR analysis is unaffected by traditional confounding factors and adheres to the standard causal sequence [23]. In this study, a Two-Sample Mendelian Randomization (TSMR) analysis was performed using summary statistics data from the IEU Open GWAS Project (IEU) [24] to assess the causal association between TI and the incidence of CA.

Data and methods

Study design

This study employed the TSMR method to investigate the genetic causal relationship between TI and CA. To explore potential variations in the effects of different tea types on CA incidence, we conducted separate TSMR analyses for each tea type. The study design was based on three fundamental assumptions: (1) IVs are independent of potential confounding factors; (2) IVs are strongly associated with the exposure variable; (3) IVs are not related to the outcome variable.

Acquisition of GWAS data

Exposure GWAS data acquisition: The GWAS data for TI, published by Ben Elsworth in 2018, was obtained from IEU (ID: ukb-b-6066). It comprised 447,485 European study subjects and encompassed 9,851,867 Single Nucleotide Polymorphisms (SNPs). The GWAS data for Green tea intake (GTI) were published by the Pan-UKB team in 2020 and obtained from IEU (ID: ukb-e-100420_CSA). It involved 1,469 South Asian study subjects without a control group and included 9,797,409 SNPs. The GWAS data for Herbal tea intake (HTI), published by the Pan-UKB team in 2020, was acquired from IEU (ID: ukb-e-100430_AFRI). This GWAS comprised 1,207 African American or Afro-Caribbean study subjects without a control group and covered 15,533,528 SNPs. The GWAS data for Rooibos tea intake (RTI), also published by the Pan-UKB team in 2020, was obtained from IEU (ID: ukb-e-100410_AFRI). It included 1,207 African American or Afro-Caribbean study subjects without a control group and covered 15,533,528 SNPs.

Outcome GWAS data acquisition: The GWAS data for CA, published by Ishigaki K in 2019, was obtained from IEU (ID: bbj-a-96). It consisted of 195,203 individuals, including 2,820 cases and 192,383 controls. The GWAS encompassed 8,885,031 SNPs. Detailed information regarding the GWAS for exposure and outcome is provided in Table 1.

Selection of instrumental variables (IVs)

To ensure the quality of IVs, we performed quality control on the GWAS summary data of TI, GTI, HTI, and RTI. Initially, we selected SNPs that showed significant association with the exposure (P < 5 × 10^-8). To address the impact of strong linkage disequilibrium, we applied a threshold of R^2 < 0.001 for linkage disequilibrium. Subsequently, SNPs with a minor allele frequency of less than 0.01 were excluded from the analysis.

MR analysis

The TSMR analysis was conducted using the TwoSampleMR package in R version 4.2.3, employing the inverse variance-weighted (IVW) method. The fixed-effects model was used when no significant horizontal pleiotropy was detected, while the random-effects model was applied in the presence of heterogeneity [25]. Additionally, MR Egger, Weighted Median, Simple Mode, and Weighted Mode were used to assess the robustness of the IVW results. To ensure the robustness of the findings, we utilized the MR-PRESSO package in R version 4.2.3 to identify and remove outliers. The mr_heterogeneity() function was employed for heterogeneity testing, with a significance threshold of P < 0.05, indicating the presence of heterogeneity. Sensitivity analysis was performed using the mr_leaveoneout() function to investigate the influence of individual SNPs on the outcome. The mr.pleiotropy.test() function was used for pleiotropy testing, with P > 0.05 indicating no significant evidence of pleiotropy.

Results

TSMR

IVs were extracted from TI, GTI, HTI, and RTI based on the criteria of P < 5 × 10^-8 and R^2 < 0.001. Specifically, 36 IVs were obtained from TI, 4 IVs from GTI, 3 IVs from HTI, and 14 IVs from RTI. Detailed information can be found in Supplementary Material 1. The TSMR results indicated no genetic causal relationship between TI and CA (IVW: OR = 1.10, 95% CI: 0.59–2.05, P = 0.772), GTI and CA (IVW:

<table>
<thead>
<tr>
<th>Category</th>
<th>Traits</th>
<th>Data sources</th>
<th>Year</th>
<th>Sample size</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>TI</td>
<td>ukb-b-60</td>
<td>2018</td>
<td>447485</td>
<td>European</td>
</tr>
<tr>
<td></td>
<td>GTI</td>
<td>ukb-e-100-420_CSA</td>
<td>2020</td>
<td>1469</td>
<td>South Asian</td>
</tr>
<tr>
<td></td>
<td>HTI</td>
<td>ukb-e-100-430_AFR</td>
<td>2020</td>
<td>1207</td>
<td>African American or Afro-Caribbean</td>
</tr>
<tr>
<td></td>
<td>RTI</td>
<td>ukb-e-100-410_AFR</td>
<td>2020</td>
<td>1207</td>
<td>African American or Afro-Caribbean</td>
</tr>
<tr>
<td>Outcome</td>
<td>CA</td>
<td>bbj-a-96</td>
<td>2019</td>
<td>195203</td>
<td>East Asian</td>
</tr>
</tbody>
</table>

Table 1 GWAS information for exposure and outcome
Table 2  Specific results of TSMR

<table>
<thead>
<tr>
<th>Exposure/Outcome</th>
<th>Nsnp</th>
<th>Methods</th>
<th>OR (95% CI)</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TI/CA</td>
<td>36</td>
<td>MR Egger</td>
<td>0.39 (0.07, 2.20)</td>
<td>0.875</td>
<td>0.295</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Weighted median</td>
<td>1.03 (0.40, 2.68)</td>
<td>0.486</td>
<td>0.945</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Inverse variance weighted</td>
<td>1.10 (0.59, 2.05)</td>
<td>0.320</td>
<td>0.772</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Simple mode</td>
<td>2.24 (0.49, 10.18)</td>
<td>0.773</td>
<td>0.304</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Weighted mode</td>
<td>1.11 (0.42, 2.92)</td>
<td>0.493</td>
<td>0.830</td>
</tr>
<tr>
<td>GTI/CA</td>
<td>4</td>
<td>MR Egger</td>
<td>0.77 (0.51, 1.15)</td>
<td>0.208</td>
<td>0.332</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Weighted median</td>
<td>1.09 (0.93, 1.28)</td>
<td>0.082</td>
<td>0.291</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Inverse variance weighted</td>
<td>1.07 (0.91, 1.26)</td>
<td>0.082</td>
<td>0.388</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Simple mode</td>
<td>1.07 (0.91, 1.27)</td>
<td>0.087</td>
<td>0.470</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Weighted mode</td>
<td>1.09 (0.92, 1.30)</td>
<td>0.087</td>
<td>0.382</td>
</tr>
<tr>
<td>HTI/CA</td>
<td>3</td>
<td>MR Egger</td>
<td>11.55 (0.88, 151.75)</td>
<td>1.314</td>
<td>0.314</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Weighted median</td>
<td>1.01 (0.92, 1.11)</td>
<td>0.047</td>
<td>0.850</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Inverse variance weighted</td>
<td>1.00(0.89, 1.13)</td>
<td>0.062</td>
<td>0.943</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Simple mode</td>
<td>0.97(0.64, 1.47)</td>
<td>0.210</td>
<td>0.908</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Weighted mode</td>
<td>1.01(0.92, 1.10)</td>
<td>0.045</td>
<td>0.841</td>
</tr>
<tr>
<td>RTI/CA</td>
<td>14</td>
<td>MR Egger</td>
<td>0.98(0.77, 1.25)</td>
<td>0.122</td>
<td>0.890</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Weighted median</td>
<td>1.02(0.94, 1.11)</td>
<td>0.041</td>
<td>0.615</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Inverse variance weighted</td>
<td>1.02(0.96, 1.09)</td>
<td>0.032</td>
<td>0.472</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Simple mode</td>
<td>1.07(0.93, 1.23)</td>
<td>0.070</td>
<td>0.366</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Weighted mode</td>
<td>1.00(0.90, 1.13)</td>
<td>0.058</td>
<td>0.936</td>
</tr>
</tbody>
</table>

Table 3  Detailed results of the heterogeneity test

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Method</th>
<th>Q</th>
<th>df</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TI</td>
<td>CA</td>
<td>Inverse variance weighted</td>
<td>35.5789</td>
<td>35</td>
<td>0.441</td>
</tr>
<tr>
<td>GTI</td>
<td>CA</td>
<td>Inverse variance weighted</td>
<td>5.058563</td>
<td>3</td>
<td>0.168</td>
</tr>
<tr>
<td>HTI</td>
<td>CA</td>
<td>Inverse variance weighted</td>
<td>3.871986</td>
<td>2</td>
<td>0.144</td>
</tr>
<tr>
<td>RTI</td>
<td>CA</td>
<td>Inverse variance weighted</td>
<td>16.4375241</td>
<td>13</td>
<td>0.226</td>
</tr>
</tbody>
</table>

OR = 1.07, 95% CI: 0.91–1.26, P = 0.388), HTI and CA (IVW: OR = 1.00, 95% CI: 0.89–1.13, P = 0.943), as well as RTI and CA (IVW: OR = 1.02, 95% CI: 0.96–1.09, P = 0.472). As shown in Table 2.

Heterogeneity test
The heterogeneity test results showed no significant heterogeneity in the genetic causal relationship between TI and CA (P = 0.441), GTI and CA (P = 0.168), HTI and CA (P = 0.144), and RTI and CA (P = 0.226). As shown in Table 3.

Sensitivity analysis
The leave-one-out sensitivity analysis was conducted, and no significant influence on the estimated causal associations between TI and CA, GTI and CA, HTI and CA, and RTI and CA was observed when individual SNPs were excluded. As shown in Figure 1.

Pleiotropy test
The results of the pleiotropy test indicate that there is no significant evidence of pleiotropy in the genetic causal relationship between TI and CA (P = 0.219), GTI and CA (P = 0.232), HTI and CA (P = 0.314), and RTI and CA (P = 0.733). As shown in Table 4.

Discussions
CA refers to the abnormal protrusion of weakened blood vessel walls in the intracranial area. A meta-analysis involving 21 countries revealed a global prevalence of approximately 3% for CA [26], with some regions showing even lower rates below 2% [27]. Limited research has been conducted on CA prevalence in China, but a study by Li et al. found a significantly higher prevalence of 7% for UCA in China compared to the international average [28]. The relationship between regional variations in CA prevalence and dietary habits remains unclear due to limitations in research methods and sample sizes. Although gender, age, and genetics have been identified as significant factors in CA development [13], there has been limited investigation into the role of dietary habits as risk factors. Tea is widely consumed worldwide [29], and TI is a popular leisure activity in Asian regions [29]. Hemodynamic stress, endothelial dysfunction, inflammatory cell infiltration, and arterial wall remodeling are recognized as major mechanisms contributing to CA development [30]. Hemodynamic stress and endothelial dysfunction have been associated with lipid levels [31], while TI, particularly GTI, has been found to significantly lower serum total cholesterol and low-density lipoprotein cholesterol concentrations [32]. These beneficial effects on lipid levels and endothelial function are attributed to the antioxidant properties of epigallocatechin gallate (EGCG) found in tea [33]. Given the observed benefits of TI in improving cardiovascular health and prolonging lifespan [34–37], there is growing interest in exploring whether TI can reduce the risk of CA occurrence.
This article presents the first MR analysis to investigate the potential genetic causal relationship between TI and CA. As an exploratory study, we found no evidence supporting a genetic causal relationship between TI and CA, and these results were consistent across different types of tea consumption (GTI, HTI, RTI). Heterogeneity and pleiotropy did not interfere with these findings.

The pathogenesis of CA remains incompletely understood, but inflammation, impaired vascular elasticity, and abnormal MMP secretion by human vascular smooth muscle cells are closely associated with CA development [38]. Among these factors, inflammation has received extensive attention [39]. Abnormal hemodynamics lead to initial vascular wall remodeling and endothelial dysfunction in aneurysms, followed by the initiation of inflammatory responses, ultimately culminating in CA formation [40–41]. Studies have reported elevated levels of high-sensitivity C-reactive protein and various interleukins in CA patients [42]. Tea’s primary active component, tea polyphenols, exhibits diverse physiological functions, including antimicrobial, anti-inflammatory, antioxidant, anticancer, hepatoprotective, intestinal protection, and cardiovascular protection properties [43]. Tea polyphenols exert their anti-inflammatory effects by inhibiting mitogen-activated protein kinases and nuclear factor-kappa B signaling pathways, and their effectiveness is dose-dependent [44]. Considering these factors, TI may have a potential role in limiting CA occurrence and development. However, our study’s findings contradict this potential possibility.

**Limitations**

This study has several limitations. Firstly, some of the GWAS data on exposure only included a single population without a control group, limiting our ability to evaluate the reverse effect of the exposure on CA. Secondly, the risk of CA increases with age, and TI habits also change with age. We could not assess the extent to which age influenced the results of both factors. Thirdly, the influence of gender on CA cannot be overlooked, and we did not address the impact of gender on the study results. Fourthly, the exposure data recorded tea consumption, but the effect of TI quantity on the outcome of CA remains unclear and may require further MR analysis. Lastly, unobserved pleiotropy was not accounted for in the study. GWAS data of exposure and outcome come from different ethnic groups, so we can not assess whether the results of this study are applicable to all populations.

**Conclusion**

Using the TSMR method, this study found no evidence of a genetic causal relationship between TI and CA, and different types of tea had no effect on CA occurrence. Further MR analysis is required to
examine the potential genetic causal relationship between the quantity of TI and CA.

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