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# Causal Relationship between Ischemic Stroke and Malignant Brain Tumors: A Two-Sample Mendelian Randomization Analysis

**Zhiyu Chen [1], Zhaoming Li [1], Yiliu Chen [2], Dianshuang Xu [1, *]**

[1] Department of Neurosurgery, The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, 510000, China
[2] College of traditional Chinese medicine, Jinan University, Guangzhou, Guangdong, 510000, China

*** Corresponding author:** Dianshuang Xu (Email: dickyhui@126.com)

**Abstract:** Object: Contemporary observational research has identified associations between cerebrovascular accidents, commonly referred to as strokes, and malignant cerebral neoplasms. However, these studies fall short of elucidating the presence of a direct causal relationship between the two conditions. In our investigation, we employ aggregated data derived from large-scale population-based genome-wide association studies (GWASs), to interrogate the potential causal linkages between these two pathologies. Method: This investigation leverages the two-sample Mendelian randomization (MR) methodology to elucidate the genetic underpinnings of the causal nexus between malignant cerebral neoplasms and ischemic cerebrovascular accidents. Rigorous quality control protocols were enacted to identify SNPs that exhibit a robust association with the exposure variable, namely malignant brain tumors. Analytical strategies, including MR-Egger regression, weighted median, inverse-variance weighted (IVW), simple mode, and weight mode methods, constituted the core of our MR analytical framework. Predominantly, the findings hinge upon the IVW method. To fortify the veracity of our conclusions, an array of sensitivity analyses such as MR-Egger regression, weighted median, MR pleiotropy, MR-PRESSO and radial MR, were deployed to meticulously evaluate heterogeneity and pleiotropy. Result: The findings derived from the IVW model reveal an absence of a significant causal nexus between malignant cerebral neoplasms and any categorization of cerebrovascular accidents, encompassing any strokes (AS) (OR 0.998, 95% CI 0.99-1.01, P=0.741), any ischemic strokes (AIS) (OR 0.999, 95% CI 0.99-1.01, P=0.999), large artery strokes (LAS) (OR 0.993, 95% CI 0.97-1.02, P=0.603), cardioembolic strokes (CES) (OR 1.012, 95% CI 0.99-1.03, P=0.275), and small vessel strokes (SVS) (OR 0.998, 95% CI 0.98-1.02, P=0.880) with respect to either an escalation or reduction in risk. Additionally, the analyses did not unveil any indications of heterogeneity or horizontal pleiotropy within the dataset. On a genome-wide scale, none of the variants associated with malignant brain tumors demonstrated relevance to the investigated outcomes. Conclusion: The outcomes of this MR investigation reveal the absence of a causal linkage between malignant cerebral neoplasms and ischemic cerebrovascular accidents. Nonetheless, the observed correlation between these two pathologies warrants attention, underscoring the necessity for heightened surveillance and care for individuals concurrently afflicted with both conditions.

**Keywords:** Strokes; Malignant Cerebral Neoplasms; Mendelian Randomization.

## 1. Introduction

When compared to other malignancies, malignant tumors of the brain typically have the worst prognosis, resulting in the greatest predicted loss of life[1]. The malignant tumors of brain are a subset of primary malignant tumors that mostly consist of gliomas, astrocytomas, oligodendrogliomas, follioblastomas, meningiomas, and other cancers, of which gliomas account for 81% of them[2, 3]. The aggressiveness[4], response to treatment[3], and likelihood of recurrence[5] of brain tumors all indicate their malignancy. Malignant brain tumors typically develop quickly, are less receptive to treatment, are difficult to entirely remove, are resistant to common treatments such as radiotherapy and chemotherapy and are prone to recurrence[3-5]. As a result, early detection and treatment are critical to improving patient survival and recovery rates. Malignant tumors of the brain may have many adverse effects on patients[6], both in themselves and during treatment of the tumor, such as neurological dysfunction as well as cognitive dysfunction. Simultaneously, the rival growth of a brain tumor may also set off the onset of other illnesses, which could have far more detrimental effects on the patient[7]. Among hospitalized patients with stroke, Nerses Sanossian et al. observed an increasing trend in the likelihood of concurrent malignancy. This went from 9.1% to 10.6% between 1997 and 2006, and a similar trend was observed in brain tumors[8]. However, the potential causal linkage between cerebral malignancies and the onset of diverse stroke types remains to be conclusively determined.

Stroke is a common neurological disease with a prevalence rate of 2.6% in China[9]. As delineated by the World Health Organization, stroke has ascended to become the primary source of adult disability and occupies the position of the second leading cause of mortality worldwide[10, 11]. According to current data, ischemic strokes are more common than hemorrhagic strokes, and ischemic strokes account for about 87% of all strokes[12]. It is known that diabetes, smoking, and hypertension are risk factors for ischemic stroke[13-15], which can be successfully avoided by leading a healthy lifestyle and following a nutritious diet[16]. The frequency of cancer patients experiencing stroke has increased, particularly among the older population[17], as a result of the shared risk factors between cancer and ischemic stroke. Consequently, the prevention of stroke in patients with cancer assumes paramount importance. Elucidating the causal linkage between ischemic stroke and glioma is imperative for advancing our comprehension of the etiology of these two conditions and is instrumental in the prevention and

management of ischemic stroke in patients with brain tumors in a clinical setting[17], and to prevent patients from having more serious consequences.

The literature has yielded contradictory results about the correlation between the risk of malignant brain neoplasm and stroke. While some studies have reported substantial connections, others have not identified any correlation. In a comprehensive multicenter cohort study dedicated to exploring the association between brain cancer and acute cerebral infarction, the findings, derived from a three-year longitudinal observation of 98,377 patients with a history of venous thromboembolism (VTE), indicated a higher propensity for cerebral hemorrhage among brain cancer patients compared to those without brain cancer[18]. Conversely from a neurologist's perspective, stroke is less common in cancer patients than metastasis or neurotoxicity induced by anticancer therapy[19]. Numerous things could be the source of the irregularity. However, in our opinion, the fact that these are all observational studies is the most important one. The presence of confounding variables cannot be ignored due to the fact that observational studies cannot prove a causal relationship between the subjects and are limited by selective bias[20]. This limitation of the research design can complicate the interpretation of results and make it difficult to make accurate inferences. This leads to studies that produce two completely opposite conclusions. Understanding the relationship between ischemic stroke and malignant neoplasm of brain is crucial for both disease prevention and management in clinical settings, as well as for our understanding of the origin of this condition.

Mendelian Randomization (MR), an increasingly recognized epidemiological research methodology, facilitates the determination of causal relationships between risk factors and outcomes by employing genetic variations, notably single nucleotide polymorphisms (SNPs), as instrumental variables (IVs)[21]. Given that the genetic instrumental variables (IVs) are randomly assorted at the time of conception, a process that precedes the onset of diseases or other environmental influences, Mendelian Randomization (MR) studies are capable of obviating residual confounding factors[22]. If exposure factors such as malignant neoplasm of brain have a causal effect on outcomes such as ischemic stroke, it is expected that genetic IVs affecting brain malignancy would also affect ischemic stroke to some extent. Additionally, owing to the employment of germline variations in MR analysis and the invariance of genetic IVs during the development or progression of the disease, MR studies serve as an invaluable instrument for mitigating the risk of reverse causality[23]. Here, we investigated the relationship between ischemic stroke and malignant brain tumors using a two-sample MR analysis based on summary data from extensive genome-wide association studies (GWASs).

# 2. Methods

## 2.1. Study Design

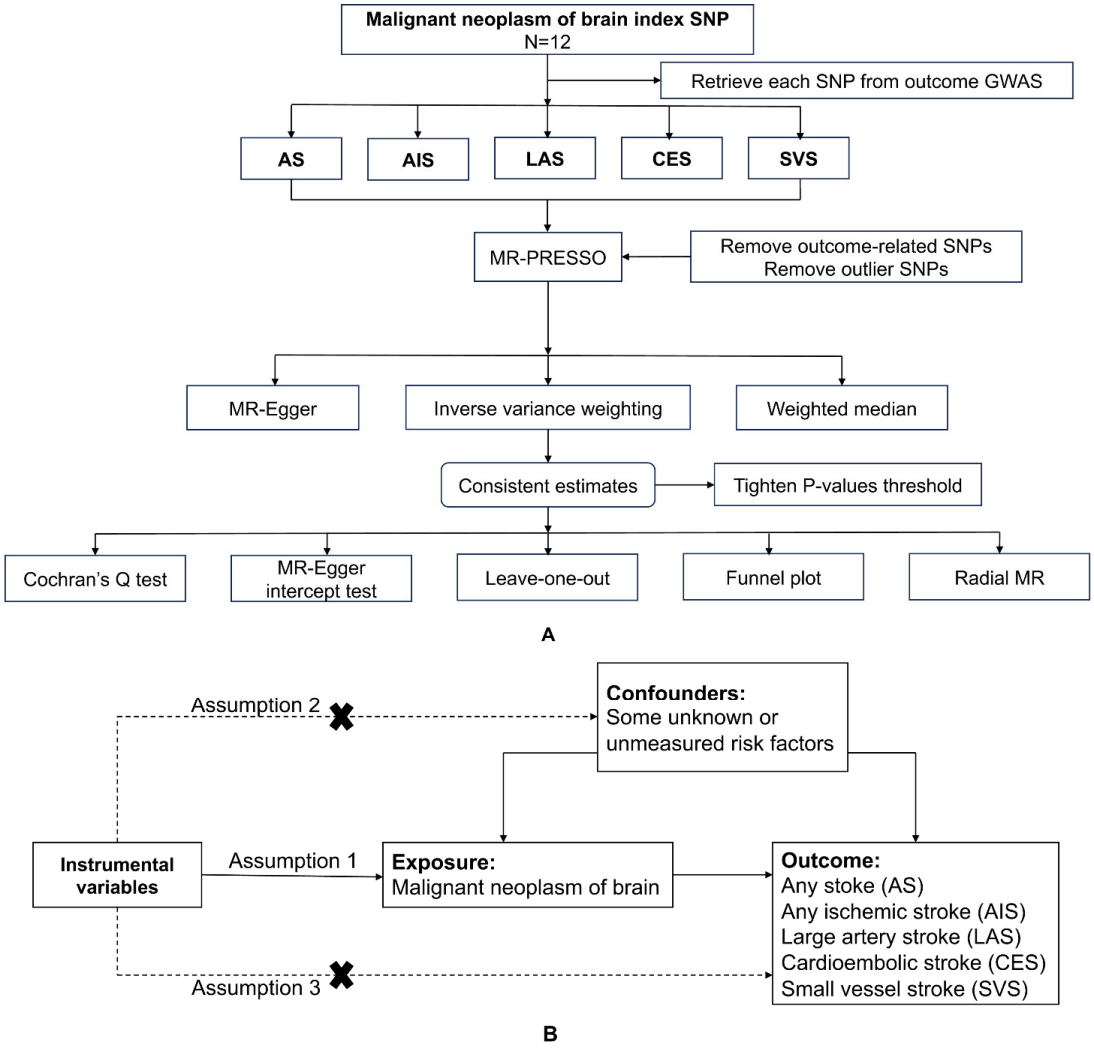



**Figure 1.** Schematic representation of an MR analysis. (A) Flow chart of study design; (B) Three assumptions for MR analysis

A two-sample MR approach was utilized to rigorously investigate the association between exposure and outcome[24]. The two-sample Mendelian randomization (MR) methodology employs data obtained from several and independent genome-wide association studies (GWASs), making it more effective and resilient in comparison to the one-sample MR strategy. In this study, Malignant neoplasm of brain was considered exposure data, whereas ischemic stroke was considered outcome data. SNPs were chosen as IVs for further investigation. Similar to randomized control trials, these separate IVs were given to the gametocyte at meiosis in a random and independent manner. Consequently, MR may be applied retroactively to identify the causal relationships between exposures and outcomes based on GWAS data[25]. As illustrated in Figure 1, In the present MR study, stroke was categorized into various subtypes: any stroke (AS), any ischemic stroke (AIS), large artery stroke (LAS), cardioembolic stroke (CES), and small vessel stroke (SVS)[26]. All original research incorporated into this MR study received authorization from the Ethics Committees of their respective universities. Additionally, informed consent was duly acquired from all participants in the initial studies. As a result, additional ethical approval is not requisite for the present MR analysis.

## 2.2. Data Sources

We received genomewide association study (GWAS) summary data from the GWAS Catalog to run two-sample MR analyses (https://www.ebi.ac.uk/gwas/). The GWAS Catalog project provided summary-level data on Malignant neoplasm of brain[27], with 110 cases and 456,238 controls included so far. The GWAS Catalog research included information on AS, AIS, LAS, CES, and SVS[28]. The dataset comprised 40,585 cases of AS with 406,111 corresponding controls, 34,217 cases of AIS also matched with 406,111 controls, 4,373 instances of LAS alongside 406,111 controls, 7,193 cases of CES with an equal number of controls, and 5,386 SVS cases paired with 192,662 controls. Every person that was enrolled had European heritage. Table 1 offers comprehensive details on the sources of the GWAS data.

## 2.3. Instrumental Variable Selection

To conduct a Mendelian randomization analysis effectively, it is imperative to adhere to three fundamental assumptions[29]: assumption one: all IVs should have a high correlation (P-value $< 5 \times 10^{-8}$, F-statistic >10) with exposure; Assumption two: all IVs must remain unimpacted by any confounders present in the relationship between exposure and outcome variables; Assumption three: all IVs should only influence exposure and not other routes in order to effect outcome. Firstly, to ensure an adequate number of SNPs for reserve MR analysis, the significance threshold for selecting instruments was established at a P-value of $5 \times 10^{-6}$, specifically for Malignant Neoplasm of the Brain. We computed the F-statistics using the formula $F = \beta^2/\sigma^2$ ($\beta$: beta for SNP-exposure impact estimate, $\sigma$: standard deviation for variation) to evaluate the potency of the chosen genetic instruments[30]. SNPs that do not satisfy $P < 5 \times 10^{-6}$ or have an F-value of less than 10 will be removed from the MR analysis. Secondly, the independence of SNPs was set using the PLINK clump approach. For clumping, we conducted linkage disequilibrium (LD) analysis with an $r^2$ threshold of less than 0.001 and a window size of 10,000 kilobases, utilizing the European cohort from the 1000 Genomes Project as our reference panel for LD. Thirdly, to ensure coherence in the genetic association analyses, we harmonized the exposure and outcome datasets so that the effect alleles were aligned consistently. Additionally, palindromic SNPs exhibiting intermediate allele frequencies were systematically excluded. Additionally, RadialMR analyses were conducted to evaluate heterogeneity. SNPs demonstrating anomalous pleiotropy with p-values less than 0.05 were systematically excluded from the study[31]. Lastly, the MR analysis was performed with the remaining SN

**Table 1.** Comprehensive elucidation of the chosen instrumental variables within the context of Mendelian randomization analysis.

| Variable | nCases | nControls | SNP | Race | Gender | Year |
|---|---|---|---|---|---|---|
| Malignant neoplasm of brain | 110 | 456,238 | 11,831,932 | European | Males and Females | 2021 |
| Any Stroke | 40,585 | 406,111 | 8,255,860 | European | Males and Females | 2018 |
| Any Ischemic Stroke | 34,217 | 406,111 | 8,340,184 | European | Males and Females | 2018 |
| Large Artery Stroke | 4,373 | 406,111 | 8,451,005 | European | Males and Females | 2018 |
| Cardioembolic Stroke | 7,193 | 406,111 | 8,306,090 | European | Males and Females | 2018 |
| Small Vessel Stroke | 5,386 | 192,662 | 8,765,828 | European | Males and Females | 2018 |

## 2.4. Statistical Analyses

In our study, we employed five distinct statistical approaches to rigorously investigate the potential causal relationship between stroke and brain malignancy, which included MR-Egger regression[32], weighted median[33], inverse-variance weighted (IVW)[34], simple mode[35], and weight mode methods[36]. Provided that all selected IVs are valid, the IVW approach is capable of generating the most precise estimates by synthesizing the Wald ratios for each SNP to deduce causal effects utilizing a meta-analytical framework[37]. Not each of IV was valid, though, in certain circumstances. Therefore, in our MR analysis, the IVW approach was the main statistical method[34]. Consequently, conducting sensitivity analyses was crucial to verify the robustness and reliability of our results. Diverse Mendelian

Randomization (MR) analyses, tailored to the specific conditions of heterogeneity and horizontal pleiotropy, were meticulously conducted. To evaluate the robustness of our findings, we employed a suite of complementary methods, including weighted mode, weighted median, and MR-Egger regression analysis. The MR-Egger approach, which incorporates an intercept term into the Egger regression model, may be used to calculate the average horizontal pleiotropy. Furthermore, even if all of the IVs are incorrect, this technique can give a valid causal estimate[32]. When 50% or more SNPs have valid IVs, the weighted median technique may produce a valid estimate[38]. Concurrently, the funnel plot analysis elucidated the presence of heterogeneity through its symmetrical distribution. To assess pleiotropic effects, we employed the MR-Egger intercept test along with the MR pleiotropy residual sum and outliers (MR-PRESSO) global test[39]. MR-PRESSO can also identify outliers in the connection and provide an estimate when they are removed. Furthermore, a leave-one-out analysis was done to investigate the impact of a single SNP on the reported outcomes[40]. Additionally, In this MR investigation, the mr_pleiotropy_test and mr_heterogeneity_test were employed to assess the presence of horizontal pleiotropy and heterogeneity, respectively[41]. Finally, The power to detect the magnitude of the current MR analysis was computed using the mRnd, which is accessible at https://shiny.cnsgenomics.com/mRnd/.[42]

The MR studies were conducted using R software (version 4.3.2) and the following packages: "TwoSampleMR", "RadialMR", and "MR-PRESSO". In the primary Mendelian Randomization (MR) analysis, a p-value below 0.05 was deemed to denote statistical significance at a nominal level.

# 3. Results

## 3.1. Instrumental Variable Selection

After removing SNPs with LD ($r^2 < 0.01$, 10,000 kb) and filtering using the significance level ($P < 5 \times 10^{-6}$), 14 SNPs were chosen for this analysis. Each of these IVs had a F-statistic more than 10 and was substantially correlated with our exposures. Subsequently, there were 2 SNPs associated with brain malignancies that could not be extracted from the resulting GWAS dataset especially those identified as AS, AIS, LAS, CES and SVS. Given the adequacy of instrumental variables (IVs), we elected not to pursue the identification of proxy SNPs. After aligning the exposure and outcome data, we removed SNPs with intermediate allele frequencies and SNPs that showed a significant association with the outcome ($P<5 \times 10^{-8}$). Phenoscanner V2 was employed to exclude SNPs associated with outcomes and covariates (p-value $< 1 \times 10^{-5}$), although no SNPs were deleted during this process. As a result, 12 SNPs were eventually listed as IVs for malignant neoplasm of brain. Supplementary Tables S1 provide the SNPs' attributes.

## 3.2. Mendelian Randomization Analyses

We included a total of SNPs closely associated with brain malignancies based on the above conditions and performed two-sample Mendelian randomization analyses with AS, AIS, LAS, CES, and SVS, respectively (Supplementary Tables S2). Figure 2 presents that malignant neoplasm of brain was not causally related to stroke or ischemic stroke or its subtypes. The risk of AS, AIS, LAS, CES, and SVS was not affected by any of the genetically predicted malignant neoplasm of brain (OR = 0.998, p-value = 0.741; OR = 0.999, p-value = 0.853; OR = 0.993, p-value = 0.603; OR = 1.012, p-value = 0.275; OR = 0.998, p-value = 0.880, respectively). The scatter plots depicted in Figure 3 similarly illustrate the estimated effect sizes of SNPs associated with malignant neoplasm of the brain on ischemic stroke and its diverse subtypes.

In MR analysis, the IVW results of the MR study primarily investigated the causal link between brain malignancy and ischemic stroke, and our findings demonstrated that brain cancer was not a risk factor for ischemic stroke.

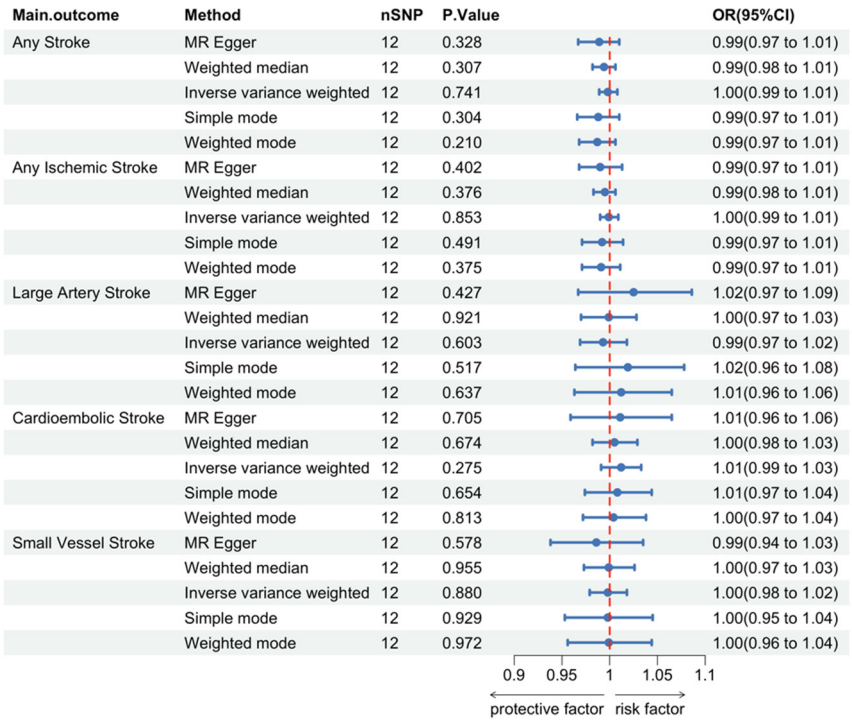



**Figure 2.** Forest plot visualizing the causal effect of AS (any stroke), AIS (any ischemic stroke), LAS (large artery stroke), CES (cardioembolic stroke) and SVS (small vessel stroke) on the risk of malignant brain neoplasm.

### 3.3. Sensitive Analysis, Heterogeneity, and Horizontal Pleiotropy Analysis

The sensitive analysis used MR-Egger and IVW (Supplementary Tables S3). The results of all five MR techniques demonstrated that there is no discernible causative relationship between the risk of malignant neoplasm of brain and AS, AIS, LAS, CES, or SVS (Figure 2). Therefore, even when based on varying numbers of valid SNPs, all five MR approaches produced consistent outcomes. The MR-Egger analysis did not find any substantial pleiotropy based on the intercept for all outcomes (intercept p-value > 0.05). The MR-PRESSO global testing indicated the absence of horizontal pleiotropy in this association (p-value > 0.05). MR analysis revealed no outliers in the MR-PRESSO data. The Cochran's Q value in the heterogeneity test indicated heterogeneity in the CES outcome (P < 0.05). Nevertheless, the IVW model was employed but did not yield any findings about CES heterogeneity. The MR-PRESSO global test could not discover indications of horizontal pleiotropy and heterogeneity in these data. No evidence of any horizontal pleiotropic effects was found in the associations between malignant neoplasm of the brain and other outcomes. Therefore, it can be assumed that there is no directional pleiotropy effect in the MR analysis. In addition, the leave-one-out test revealed that the results of our MR analysis remained unchanged even when considering a single SNP (Figure 4), indicating that this result was reliable and stable. The funnel plots are depicted in Supplementary Figure S1.

### 3.4. Radial MR Analysis

The possible outlier SNPs were investigated using radial MR analysis. There are a few potential outliers. SNPs could potentially impact our observations while investigating the causal connection between brain malignant neoplasms and the risk of AS, AIS, LAS, CES, and SVS. However, the F-statistics (p-value > 0.05) and Q-statistics (p-value > 0.05) indicated that the overall effect size is stable and not varied. (Supplementary Tables S4) Furthermore, every sensitivity analysis produced consistent results, indicating that the presence of these outlier SNPs would not alter our findings.

## 4. Discussion

This is the first study to use MR design to investigate the causative relationships between the risk of AS, AIS, LAS, CES, and SVS and genetically predicted malignant brain neoplasms. Furthermore, our findings demonstrated that neither the risk of AS, AIS, LAS, CES, or SVS nor any malignant brain tumors had any causative involvement.

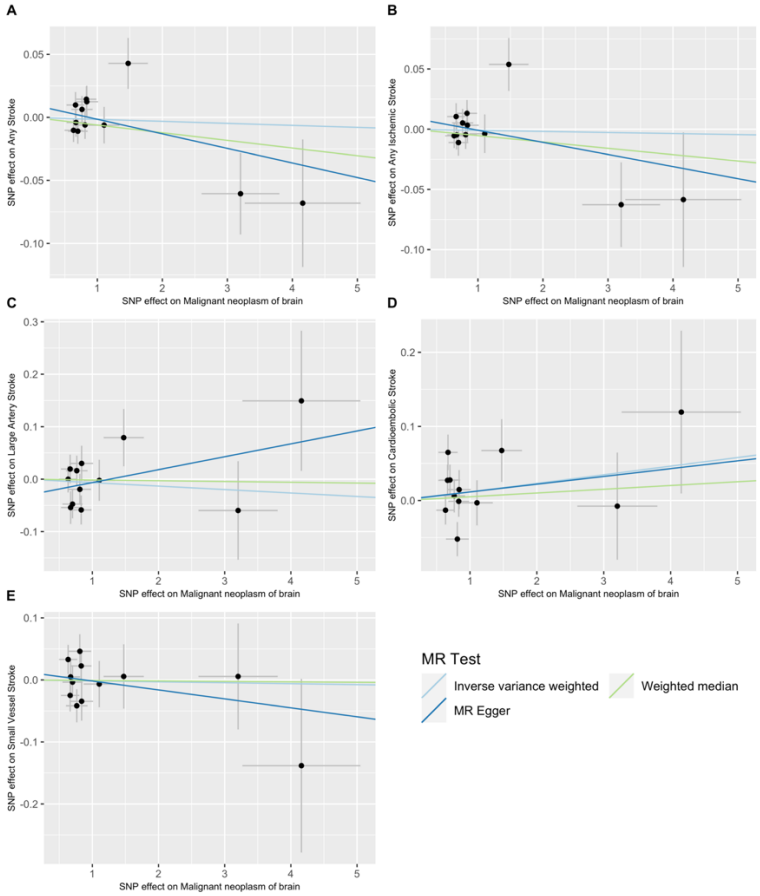



**Figure 3.** The scatter plots of associations between genetically predicted malignant brain neoplasm, and strokes. (A) The scatter plot of the causality between malignant brain neoplasm and AS; (B) The scatter plot of the causality between malignant brain neoplasm and AIS; (C) The scatter plot of the causality between malignant brain neoplasm and LAS; (D) The scatter plot of the causality between malignant brain neoplasm and CES; (E) The scatter plot of the causality between malignant brain neoplasm and SVS.

Although studies have confirmed the association between several types of cancer and ischemic stroke, no randomized controlled studies or MR analyses have been performed to extend this association between the two diseases[43]. Numerous observational studies have scrutinized the correlation between hemorrhagic or ischemic stroke and the

risk or prognosis associated with cerebral malignancies. However, a unified consensus on this correlation remains elusive due to divergences in the results of these investigations.

The extant body of research literature addressing stroke incidence in individuals with primary brain tumors is notably constrained, with the majority of these studies primarily concentrating on ascertaining risk factors and conspicuously omitting the inclusion of cerebral malignancy as a risk factor for ischemic stroke. A systematic review and meta-analysis by Turner M et al. revealed that head and neck cancers are significantly associated with an increased incidence of stroke (HR 1.54 (95% CI 1.40-1.69), hemorrhagic), especially within the first six months following diagnosis[44]. It is currently believed that brain malignancies lead to stroke development possibly due to changes in the tumor cell micro-environment causing the secretion of various cytokines[45, 46], along with primary brain malignancy patients potentially facing tumor-induced compression of local blood vessels, cancer-induced vascular erosion, and secretion of autocrine factors by the tumor triggering blood coagulation, all of which may contribute to the development of stroke in patients with malignant brain cancers[47]. Ischemic stroke may result in significant disability among cancer patients, and the presence of cancer has been shown to escalate the risk of ischemic stroke. However, this correlation has not been conclusively extended to encompass brain tumors[48].

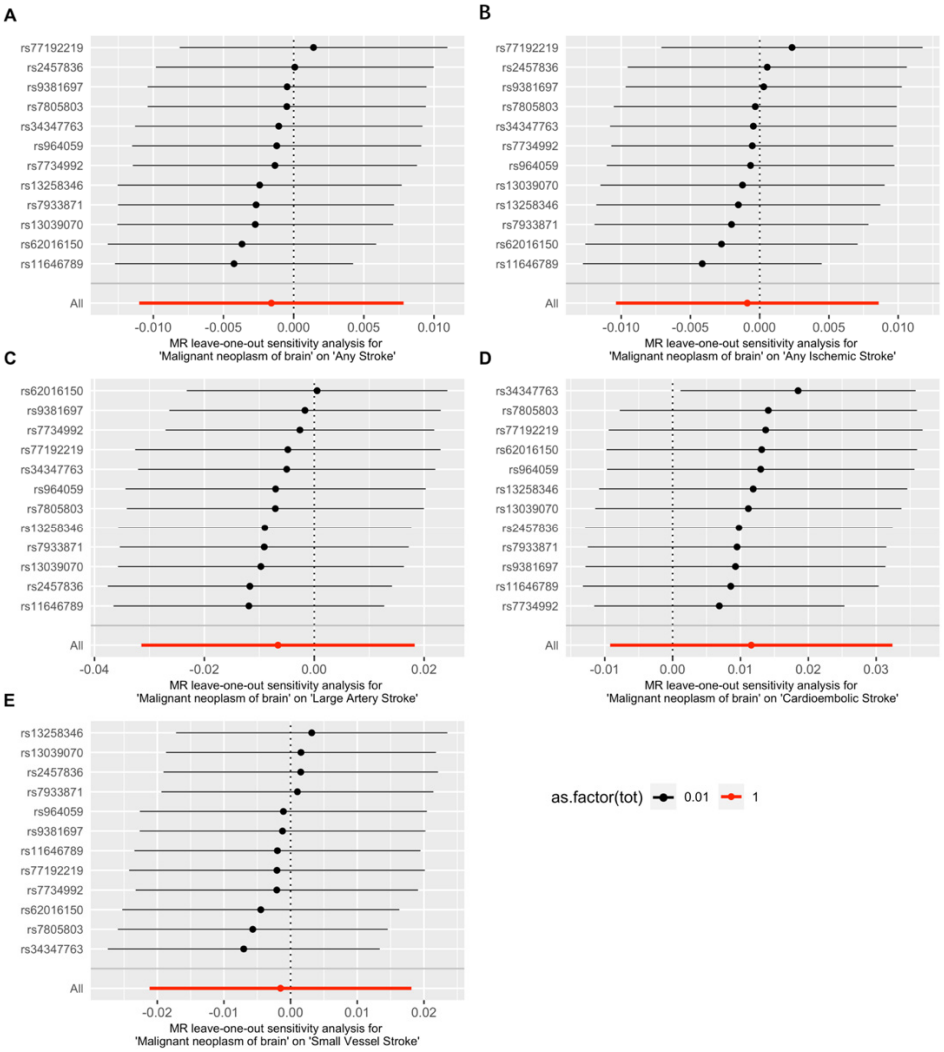



**Figure 4.** The leave-one-out sensitivity analysis of MR analysis. (A) The leave-one-out sensitivity analysis of the causality between malignant brain neoplasm and AS; (B) The leave-one-out sensitivity analysis of the causality between malignant brain neoplasm and AIS; (C) The leave-one-out sensitivity analysis of the causality between malignant brain neoplasm and LAS; (D) The leave-one-out sensitivity analysis of the causality between malignant brain neoplasm and CES; (E) The leave-one-out sensitivity analysis of the causality between malignant brain neoplasm and SVS.

Hypoxia is the pathophysiological foundation common to the development of both stroke and brain tumors. This is particularly significant because factors such as cerebral vascular invasion or blood flow obstruction caused by malignant brain tumors not only constitute a direct threat to brain health but also further exacerbate the adverse effects of stroke or brain tumors[49]. In this context, we can observe a critical aspect of brain tumor development: Tumor cells undergo rapid proliferation, accompanied by the rapid growth of blood vessels, due to the high consumption of oxygen and abnormal substance metabolism by the cells. This rapid proliferation and the formation of new blood vessels, although a strategy for the survival of the tumor cells, prevents cells deep within the tumor tissue from receiving sufficient nutrients, ultimately leading to necrosis[50]. This process not only exacerbates the deterioration of the tumor itself and rapid changes in tumor structure, but also creates conditions conducive to the rupture or obstruction of cerebral

vessels. Furthermore, in tumor patients, especially those with brain tumors, the risk of hemorrhage is significantly increased, along with the occurrence of a hypercoagulable state, which markedly raises the risk of stroke[51]. This situation further illustrates the potential connection between malignant brain tumors and hemorrhagic or ischemic stroke. Therefore, it can be seen that there may be a certain degree of association between malignant brain tumors and hemorrhagic or ischemic strokes, reflecting their shared pathophysiological basis and the possibility of mutual influence. However, our MR research did not identify any causal link between genetically predicted malignant neoplasm of the brain and the occurrence of stroke.

A number of retrospective studies have likewise undertaken assessments to elucidate the potential association between individuals diagnosed with cerebral malignancies and those experiencing stroke. A retrospective study by Cestari DM et al. indicates that thrombotic stroke is the most common cause of stroke in cancer patients, with brain tumors accounting for 9% of these cases[52]. Findings from a detailed patient-level meta-analysis revealed that the continued use of aspirin for cerebrovascular disease did not lead to a statistically significant elevation in cancer incidence. However, an augmented risk of cerebral hemorrhage was observed in patients upon the adjunctive use of clopidogrel[53]. Additionally, Adams HP Jr et al. noted that both hemorrhagic and ischemic strokes can facilitate the metastasis of brain tumors and lead to treatment resistance. The study also shows that despite the declining hospitalization rate for stroke patients, the risk of developing cancer has not significantly decreased[54]. A cohort study by Zaorsky et al, using data on 99,343 brain tumor patients from the SEER database showed that the risk of fatal strokes occurring in patients with brain tumors compared with all other patients was not significantly different compared with those at other sites[55]. Clinical retrospective analyses carried out by Cestari DM and colleagues, along with Zhang et al., discerned no substantial divergence in the vascular risk profiles between cancer patients and a substantial cohort of stroke patients. This implies that cancer may not exert a pivotal influence in the pathology of stroke patients[52, 56].

Observational studies investigating the correlation between ischemic stroke and various malignancies, such as malignant brain tumors, have produced inconclusive findings, possibly attributable to several causes. Investigations into the correlations between ischemic stroke and numerous tumors, encompassing malignant brain tumors, have revealed indeterminate outcomes, potentially due to an array of underlying reasons[57-60]. Initially, observational studies are susceptible to multiple limitations, such as selection bias, recall bias, and confounding factors. Bias emerges in the estimation of the relationship between exposure and outcome variables when the study cohort inadequately represents the general population. Recall bias occurs when participants misclassify their exposure status, stemming from challenges in precisely recalling past exposures. Confounding transpires when erroneous associations between exposure and outcome variables are influenced by external variables. Additionally, observational studies often grapple with limited sample sizes, consequently diminishing their statistical power to discern authentic associations between exposure and outcome variables. This limitation can result in divergent conclusions across different studies. Thirdly, observational research frequently relies on self-reported data, which may introduce social desirability bias. Rather than accurately representing their actual exposures or behaviors, participants may report responses they deem socially acceptable.

Our findings indicate that there is no direct causal relationship between malignant brain tumors and the occurrence of ischemic strokes. However, this does not imply that patients with concurrent brain cancer and strokes can be disregarded. Coping with both of these severe and fatal diseases poses a significant challenge to an individual's health. From pathophysiology to clinical manifestations, and further to treatment options and outcomes, the stroke occurrences in cancer patients may differ in various aspects from those in the general population[61]. Compared to other types of strokes, tumor-related ischemic stroke has a significantly poorer prognosis, with significantly higher rates of death and recurrence. For example, the mortality rate in tumor patients post-ischemic stroke exhibits a 3.3% increase at one month and a 45.6% increase at one year, in comparison to the general population. This substantial increment markedly diminishes the median survival duration of these patients[62, 63]. It is precisely because patients suffer from both of these severe diseases that those with concurrent cancer and stroke have an even poorer prognosis[56, 64]. Consequently, patients with concurrent brain tumors and strokes require heightened attention due to their poorer prognosis and typically unfavorable response to clinical treatment. Therefore, it is necessary to further investigate the potential correlations between these conditions.

The current Mendelian randomization analysis has a number of advantages: first, the current investigation used a two-sample MR design to limit the interference of confounding variables and inverse relationships in standard observational studies. Second, the accurateness of the data was guaranteed since all IVs subjected to MR analysis were rigorously screened and all F-statistics were more than 10. Lastly, the sensitivity, heterogeneity, and horizontal pleiotropy were tested using a variety of approaches. The results of each test demonstrated the robustness and stability of the relationship between malignant brain neoplasm and ischemic stroke.

However, there were several possible shortcomings with the current MR. Firstly, this MR only utilized summary-level statistics, with individual-level data remaining unutilized. As a result, this limitation precludes our ability to examine the gender-specific associations between different subtypes of stroke, such as ischemic stroke, and the risk of cerebral malignancy. Secondly, every participant in our MR analysis was European ancestry. Because different ancestry populations have different genetic variances, more research is needed to determine whether these correlations existed in other ancestry communities. Thirdly, the p-value threshold for malignant brain neoplasm was adjusted to $5\times10^{-06}$ in order to get additional SNPs for reverse MR studies. This means that several IVs had very modest proportions of variance explained. Fourthly, because of the canalization and robustness in human genetics and illness, contemporary MR data should be interpreted with greater caution. Fifthly, although we utilized MR-Egger intercept and MR-PRESSO global test to identify and account for pleiotropy in genetic variations, it is possible that confounding factors such as lifestyle, personality, and gender between exposure and outcome may still be present, which could introduce bias into our findings. Finally, the extent of sample overlap remains uncertain due to the absence of comprehensive information

regarding the GWAS studies included, potentially biasing our results. Considering the inherent constraints of GWAS data, it becomes imperative to undertake further research endeavors to more comprehensively comprehend the potential mechanisms elucidating these causal relationships.

# 5. Conclusion

In summary, the outcomes of our analysis did not furnish substantial evidence to substantiate a causal link between cerebral malignancies and conditions including AS, AIS, LAS, CES, and SVS. Consequently, endeavors to mitigate the risk of ischemic stroke or cerebrovascular incidents by precluding the onset of malignant brain tumors may prove ineffectual. It is imperative to investigate alternative methods to diminish the incidence of ischemic strokes.

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