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ORIGINAL RESEARCH

Lack of a Causal Association between DNA Methylation GrimAge Acceleration and Brain Tumor Incidence: A Two-Sample Mendelian Randomization Study

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Objective: To investigate the potential causal relationship between DNA methylation GrimAge acceleration (GAA) and brain tumor incidence using a two-sample Mendelian randomization (MR) approach.

Methods: We leveraged publicly available genome-wide association study (GWAS) summary data for GAA (34,467 participants) and brain tumor incidence (491,542 participants). Twenty-six single nucleotide polymorphisms (SNPs) served as instrumental variables for GAA. Inverse variance weighted (IVW) was the primary method, complemented by MR-Egger, weighted median, simple mode, and weighted mode. Sensitivity analyses tested heterogeneity and pleiotropy.

Results: The IVW analysis indicated no significant causal effect of GAA on brain tumor risk ($\beta = -0.006$, $p = 0.908$). Other MR methods concurred. Sensitivity checks, including heterogeneity and MR-Egger intercept tests, supported these null findings.

Conclusion: Our results do not support a causal association between GrimAge acceleration and brain tumor incidence. Accelerated epigenetic aging, as measured by GAA, may not be a direct driver of brain tumor risk. Further investigations should explore other epigenetic or genetic factors implicated in brain tumor etiology.

Keywords: DNA methylation, GrimAge acceleration, brain tumor, Mendelian randomization, causal inference, epigenetics, cancer risk

Introduction

Brain tumors represent a significant global health burden, with an estimated 308,102 new cases and 251,329 deaths worldwide in 2020.[1] These neoplasms encompass a diverse group of tumors, ranging from benign to highly malignant, each with unique clinical presentations and outcomes.[2] Despite advances in treatment modalities, including surgery, radiation therapy, and chemotherapy, the prognosis for many brain tumor patients remains poor, underscoring the critical need for improved understanding of tumor etiology and novel therapeutic approaches.[3]

The etiology of brain tumors is complex and multifactorial, involving both genetic and environmental factors. While certain genetic syndromes and exposure to high-dose ionizing radiation are established risk factors, they account for only

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a small proportion of cases.[4] In recent years, epigenetic alterations have emerged as crucial players in cancer development and progression, offering new insights into the molecular mechanisms underlying brain tumorigenesis.[5]

DNA methylation, a key epigenetic modification, has garnered significant attention in cancer research. This process involves the addition of methyl groups to cytosine residues in CpG dinucleotides, influencing gene expression and chromatin structure.[6] Aberrant DNA methylation patterns have been observed in various cancer types, including brain tumors, suggesting a potential role in tumor initiation and progression.[7]

The concept of epigenetic age, derived from DNA methylation patterns, has provided a novel perspective on biological aging and its relationship to disease risk. Epigenetic age acceleration, which occurs when an individual's epigenetic age exceeds their chronological age, has been associated with increased mortality and morbidity across various health conditions.[8] Recent studies have explored the relationship between epigenetic age acceleration and cancer risk, with some evidence suggesting a potential link to brain tumor development.[9]

Among the various epigenetic age measures, DNA methylation GrimAge acceleration (GAA) has emerged as a robust predictor of age-related morbidity and mortality.[10] Developed through a combination of DNA methylation-based surrogate biomarkers for plasma proteins and smoking pack-years, GAA has shown stronger associations with age-related outcomes compared to other epigenetic age measures.[11] However, the causal nature of the relationship between GAA and brain tumor risk remains unclear, necessitating further investigation.

Mendelian randomization (MR) has emerged as a powerful tool in genetic epidemiology, enabling researchers to infer causal relationships between exposures and outcomes using genetic variants as instrumental variables.[12] This approach leverages the random assortment of genetic variants during meiosis, mitigating concerns of confounding and reverse causation that often plague observational studies.[13] Two-sample MR, which utilizes summary-level data from separate genome-wide association studies (GWAS) for the exposure and outcome, has further expanded the applicability of this method in large-scale epidemiological investigations.[14]

The application of MR in cancer epidemiology has provided valuable insights into potential causal risk factors for various cancer types.[15] However, the use of this approach in brain tumor research, particularly in investigating the causal role of epigenetic factors, remains limited. Given the complexity of brain tumor etiology and the potential importance of epigenetic mechanisms in their development, applying MR to explore the causal relationship between DNA methylation age acceleration and brain tumor risk represents a promising avenue of investigation. Here, we examine whether GAA causally influences brain tumor risk, addressing gaps left by observational research.

Methods

Study Design and Data Sources

This study employed a two-sample Mendelian randomization (MR) approach to investigate the potential causal relationship between DNA methylation GrimAge acceleration (GAA) and brain tumor incidence. We utilized summary-level data from two large-scale genome-wide association studies (GWAS) to obtain genetic instruments for the exposure (GAA) and outcome (brain tumor incidence).

For the exposure data, we used the GWAS results from a study on DNA methylation GrimAge acceleration (ebi-a-GCST90014288), which included 34,467 participants. The outcome data were derived from a GWAS on brain tumor incidence (ebi-a-GCST90018800), comprising 491,542 individuals. Both datasets were obtained from publicly available repositories, ensuring compliance with ethical guidelines and data protection regulations.

Selection of Genetic Instruments

To select genetic instruments for GAA, we applied the following criteria: (1) single nucleotide polymorphisms (SNPs) associated with GAA at genome-wide significance ($p < 5\times10^{-8}$); (2) independence between SNPs, achieved through linkage disequilibrium (LD) pruning ($r^2 < 0.001$, window size = 10,000 kb); and (3) absence of palindromic SNPs with intermediate allele frequencies (0.3 < minor allele frequency < 0.7) to avoid potential strand ambiguity issues.

After applying these criteria, we identified 26 independent SNPs as instrumental variables for GAA. For each selected SNP, we extracted the following information from both GWAS datasets: SNP identifier (rsID), effect allele, other allele, effect allele frequency, beta coefficient, standard error, and p-value.

Statistical Analysis

We performed MR analyses using five different methods to assess the robustness of our findings: inverse variance weighted (IVW), MR-Egger, weighted median, simple mode, and weighted mode. The IVW method served as our primary analysis, providing an estimate of the causal effect by combining the ratio estimates from each SNP, weighted by the inverse of their variance.

The MR-Egger method was used to assess potential directional pleiotropy and provide a pleiotropy-adjusted causal estimate. The weighted median method, which provides a consistent estimate when up to 50% of the weights come from invalid instruments, was employed to evaluate the stability of our results. Simple mode and weighted mode methods, which are robust to outliers and invalid instruments, were used to further assess the consistency of our findings.

We calculated the causal effect estimates (β) and their corresponding 95% confidence intervals (CIs) for each MR method. The effect estimate represents the change in brain tumor risk per standard deviation increase in GAA. Statistical significance was set at a two-sided p-value < 0.05.

Sensitivity Analyses

To evaluate the validity of our genetic instruments and the robustness of our results, we conducted several sensitivity analyses. First, we assessed heterogeneity among the causal estimates of individual SNPs using Cochran's Q statistic for the IVW and MR-Egger methods. Significant heterogeneity ($p < 0.05$) would suggest potential violations of the MR assumptions.

Second, we performed a leave-one-out analysis to identify any influential outliers that might drive the overall effect estimate. This involved sequentially removing each SNP from the analysis and recalculating the IVW estimate to assess the impact on the overall results.

Third, we created a funnel plot to visually inspect the symmetry of individual SNP effects, which can help detect potential directional pleiotropy. Asymmetry in the funnel plot might indicate the presence of pleiotropy or other violations of MR assumptions.

Lastly, we conducted a horizontal pleiotropy analysis using the MR-Egger intercept test. A significant non-zero intercept ($p < 0.05$) would suggest the presence of directional pleiotropy, potentially violating the MR assumptions.

All statistical analyses were performed using the "TwoSampleMR" package in R (version 4.0.3). Plots were generated using the "ggplot2" package to visualize the results of our MR analyses and sensitivity tests.

Results

Mendelian Randomization Framework

Figure 1 illustrates the conceptual framework of our Mendelian randomization (MR) analysis. This diagram depicts the relationship between the instrumental variables (SNPs), the exposure (DNA methylation GrimAge acceleration), and the outcome (brain tumor incidence). The figure highlights the key paths in MR analysis: Path A shows the association between SNPs and the exposure, Path B represents the potential causal effect under investigation, while Paths C and D illustrate potential violations of MR assumptions through confounding and horizontal pleiotropy, respectively. This framework underpins our approach to inferring the causal relationship between DNA methylation GrimAge acceleration and brain tumor risk.

Genetic Instruments for DNA Methylation GrimAge Acceleration

Our analysis identified 26 independent single nucleotide polymorphisms (SNPs) as valid instrumental variables for DNA methylation GrimAge acceleration (GAA). These SNPs, strongly associated with GAA ($p < 5\times10^{-8}$), demonstrated no significant linkage disequilibrium ($r^2 < 0.001$). Table S1 presents the characteristics of these SNPs, including their chromosomal positions, effect sizes (beta coefficients), standard errors, and p-values for their association with GAA. The effect allele frequencies ranged from 0.0118 to 0.7035, representing a diverse set of common and less common variants.

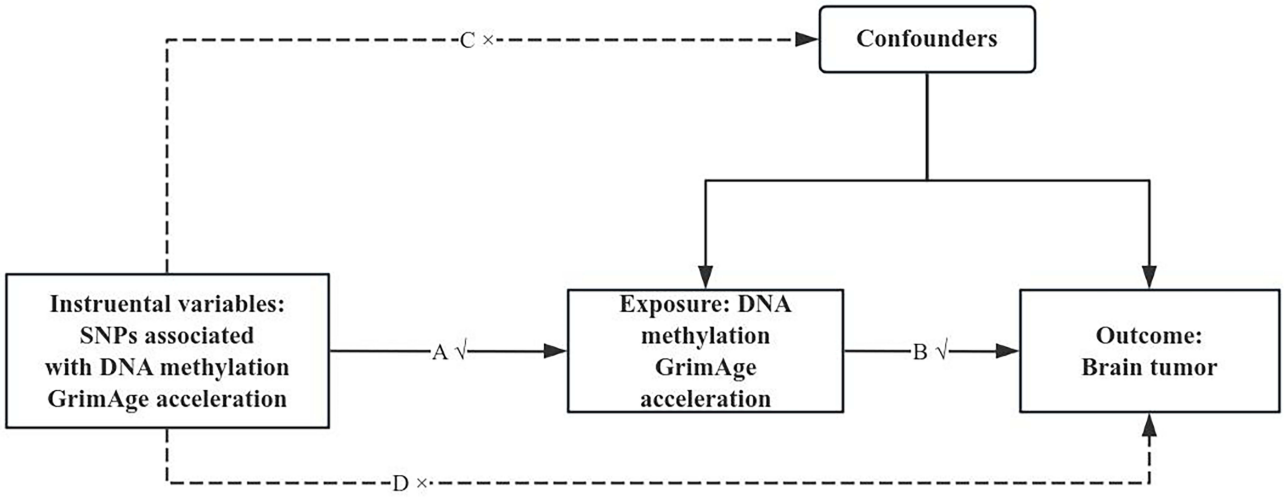

Figure 1 The process of MR-analysis.

Notably, rs9386796 on chromosome 6 showed the strongest association (β = 0.1983, SE = 0.0294, p = 1.64×10^{-11}), while rs148545630 on chromosome 6 exhibited the largest effect size (β = 1.0581, SE = 0.2214, p = 1.75×10^{-6}).

Mendelian Randomization Analysis

The primary inverse variance weighted (IVW) analysis revealed no significant causal effect of GAA on brain tumor risk (β = −0.006, 95% CI: −0.110 to 0.098, p = 0.908). This result suggests that a one standard deviation increase in GAA is not associated with a significant change in the log odds of brain tumor incidence. Table S2 summarizes the results from multiple MR methods, all consistently indicating no significant causal relationship. The MR-Egger method yielded a slightly positive, but non-significant effect (β = 0.057, 95% CI: −0.249 to 0.364, p = 0.716), while the weighted median approach produced results similar to the IVW method (β = −0.009, 95% CI: −0.153 to 0.135, p = 0.905). Simple mode and weighted mode analyses further corroborated these findings with non-significant effect estimates.

Figure 2 visualizes these results in a scatter plot, depicting the SNP effects on GAA against their effects on brain tumor risk. The plot includes regression lines representing different MR methods, all of which cluster around a slope of zero, reinforcing the lack of a significant causal relationship.

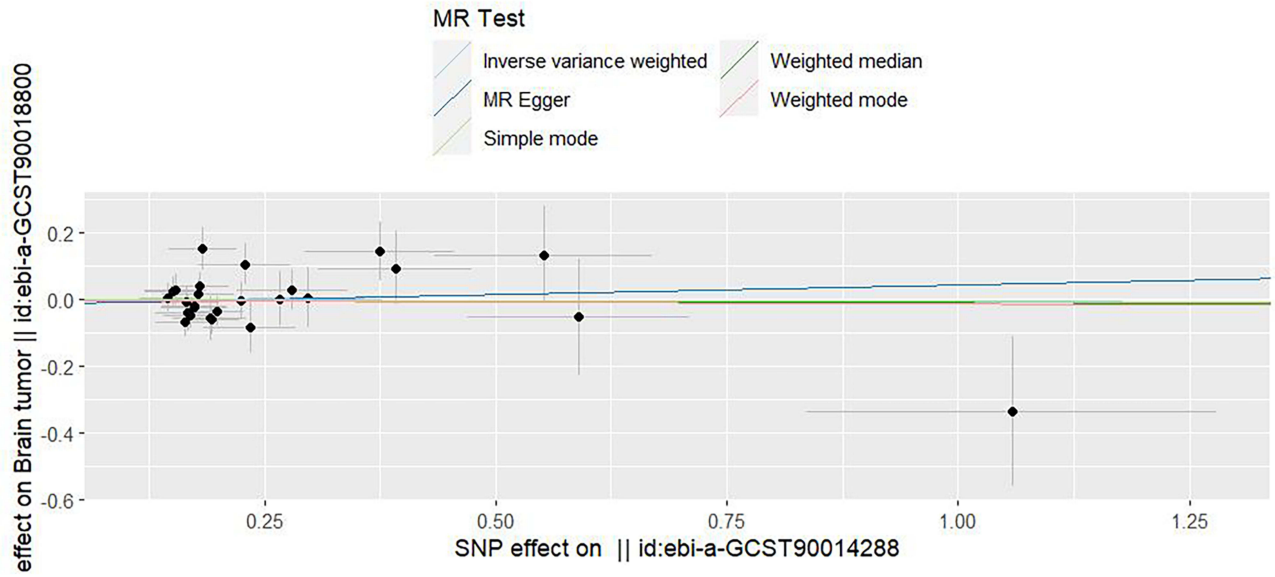

Figure 2 Scatter plot of the MR analysis.

Table 1 Sensitivity Analysis

Exposure	Pleiotropy Test			Heterogeneity Test			
	MR-Egger			MR-Egger		IVW	
	Intercept	SE	P	Q	Q_pval	Q	Q_pval
DNA methylation GrimAge acceleration	−0.0140	0.0323	0.6686	25.685	0.3692	25.886	0.4136

Sensitivity Analyses

Heterogeneity tests, as shown in Table 1, revealed no significant heterogeneity among the causal estimates of individual SNPs. The IVW Q-statistic (25.886, p = 0.414) and MR-Egger Q-statistic (25.685, p = 0.369) both support the consistency of our results across different genetic instruments. The MR-Egger intercept test did not indicate significant directional pleiotropy (intercept = −0.0140, SE = 0.0323, p = 0.669), suggesting that the basic assumptions of MR analysis were not violated.

The leave-one-out analysis, visualized in Figure 3, demonstrated the robustness of our findings. The plot shows that the causal effect estimate remained consistently non-significant regardless of which SNP was removed from the analysis, indicating that no single SNP had a disproportionate influence on the overall result.

Figure 4 presents a funnel plot of the MR analysis, displaying a symmetrical distribution of individual SNP effects around the point estimate. The SNPs are scattered on both sides of the vertical line representing the overall effect estimate, with precision (inverse of the standard error) ranging approximately from 3.0 to 4.5. This symmetry further supports the absence of directional pleiotropy and strengthens the validity of our MR assumptions.

Figure 5 provides a forest plot of the individual SNP effects on brain tumor risk. The plot illustrates that most SNPs had small effect sizes clustered around zero, with their 95% confidence intervals crossing the null line. This visualization reinforces the overall finding of no significant causal effect of GAA on brain tumor risk.

SNP-Specific Effects

Table S3 details the effects of each SNP on the outcome (brain tumor incidence). The majority of SNPs showed small, non-significant effects on brain tumor risk, consistent with the overall null finding. For instance, rs887466 on

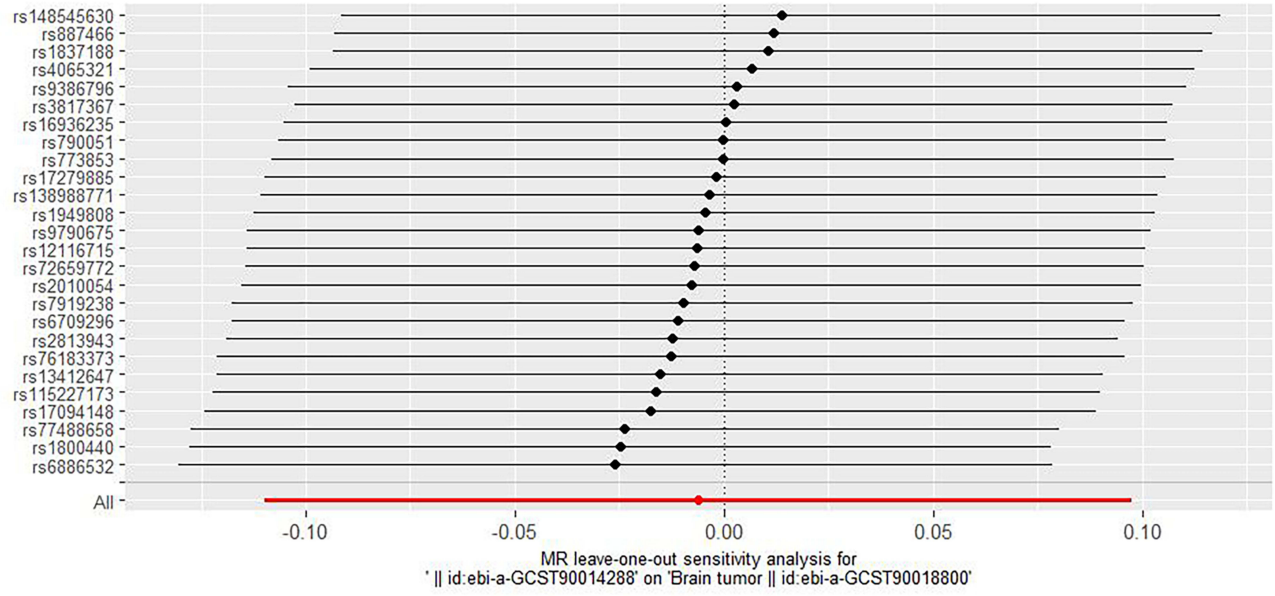

Figure 3 Leave-one-out plot of the MR analysis.

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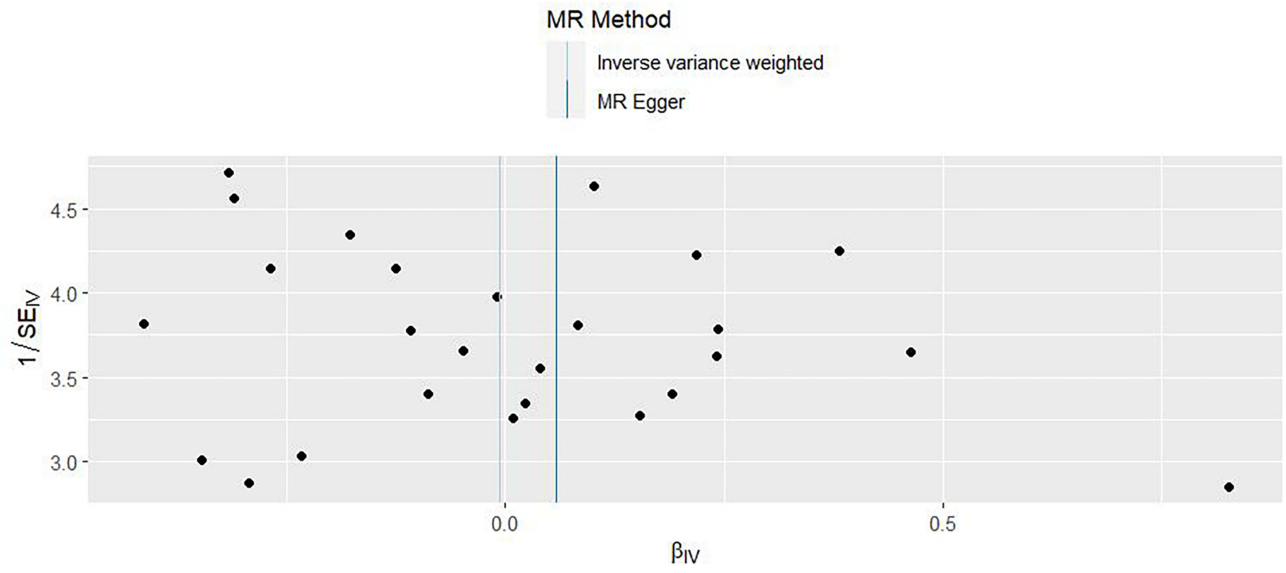

Figure 4 Funnel plot of the MR analysis.

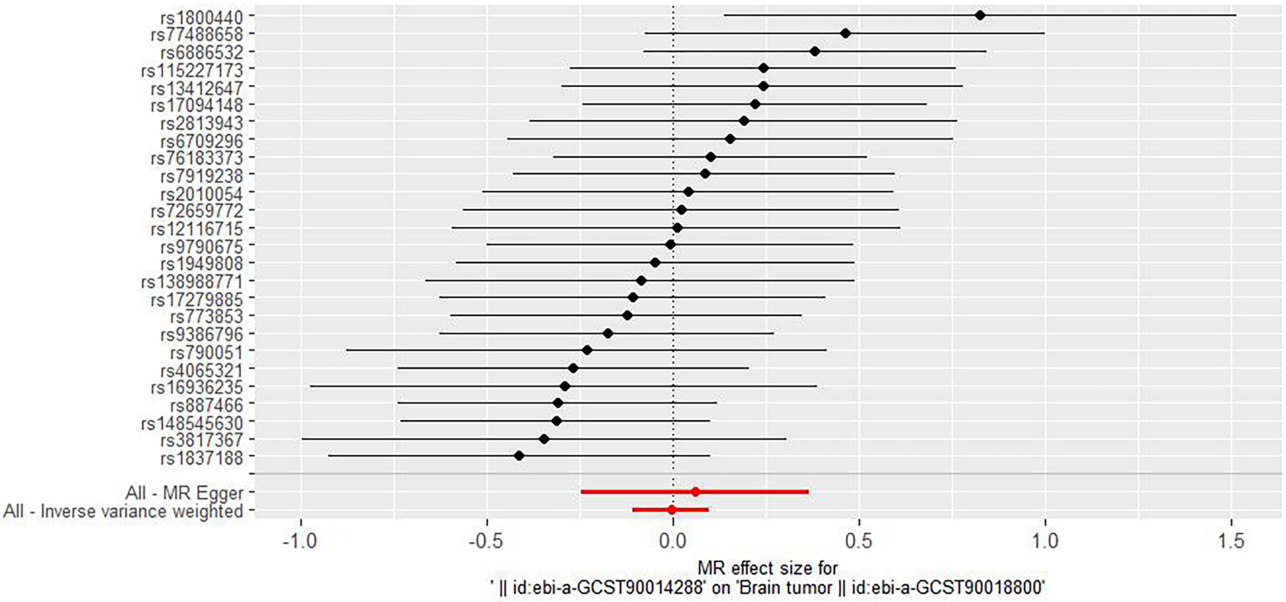

Figure 5 Forest plot of the MR analysis.

chromosome 6 had a small positive effect (β = 0.0597, SE = 0.0423, p = 0.1581), while rs9386796 on chromosome 6 showed a slight negative effect (β = −0.0352, SE = 0.0456, p = 0.4398). The SNP with the largest effect, rs148545630 on chromosome 6, still did not reach statistical significance (β = −0.3344, SE = 0.2243, p = 0.1359).

Discussion

This two-sample Mendelian randomization study found no evidence of a causal relationship between DNA methylation GrimAge acceleration (GAA) and brain tumor risk. Our findings, derived from large-scale genetic data and robust across multiple MR methods, suggest that accelerated epigenetic aging, as measured by GAA, may not play a direct causal role in brain tumor development.

The absence of a significant causal association between GAA and brain tumor risk contrasts with some previous observational studies that have reported links between epigenetic age acceleration and cancer risk.[16] For instance,

a recent epigenome-wide association study found that accelerated DNA methylation age was associated with increased risk of several cancer types, including brain tumors.[17] However, such observational studies are prone to confounding and reverse causation, highlighting the importance of causal inference methods like MR.

Our null findings align with some recent MR studies investigating the causal role of epigenetic age acceleration in other cancer types. For example, a large-scale MR study found no evidence of a causal effect of epigenetic age acceleration on overall or site-specific cancer risk, including lung, breast, and colorectal cancers.[18] These consistent null findings across different cancer types suggest that the observed associations in observational studies may be due to confounding factors or reverse causation rather than a direct causal effect of accelerated epigenetic aging.

The lack of a causal relationship between GAA and brain tumor risk does not negate the importance of epigenetic mechanisms in brain tumor biology. Numerous studies have demonstrated significant alterations in DNA methylation patterns in brain tumors, including global hypomethylation and gene-specific hypermethylation.[19] These epigenetic changes play crucial roles in tumor initiation, progression, and treatment response.[20] Our findings suggest that while epigenetic alterations are important in brain tumor biology, accelerated epigenetic aging itself may not be a direct causal factor in tumor development.

One potential explanation for our null findings is that GAA may be a marker of general health status and cumulative environmental exposures rather than a direct causal factor for specific diseases.[21] GAA incorporates information from DNA methylation-based surrogate biomarkers for plasma proteins and smoking pack-years, which may reflect overall physiological dysregulation and lifestyle factors.[10] While these factors may contribute to cancer risk through various pathways, our results suggest that their cumulative effect, as captured by GAA, does not directly influence brain tumor development.

The strengths of our study include the use of large-scale genetic data, multiple MR methods, and comprehensive sensitivity analyses. The two-sample MR design allowed us to leverage summary statistics from large GWAS studies, increasing statistical power and reducing potential bias from sample overlap.[22] Our use of multiple MR methods and sensitivity analyses, including tests for heterogeneity and pleiotropy, enhances the robustness of our findings.

Notably, two SNPs showed nominal significance but did not withstand stringent correction or sensitivity testing. They neither caused major heterogeneity nor shifted the overall null effect. Their role may relate to underlying genetic variation in DNA methylation patterns unrelated to tumorigenesis. Although GAA captures aging-related processes, these results imply it may not be a direct driver of brain tumor initiation. Epigenetic mechanisms (eg, local hypermethylation in tumor suppressor genes) could be more pertinent than global aging measures. GAA may serve primarily as an integrative biomarker of health status, rather than a specific tumor risk factor.

However, several limitations should be considered when interpreting our results. First, MR analysis relies on specific assumptions, including the absence of horizontal pleiotropy. While our sensitivity analyses did not indicate significant violations of these assumptions, we cannot completely rule out the possibility of residual pleiotropy. Second, our study focused on overall brain tumor risk and did not differentiate between specific brain tumor subtypes due to data limitations. Different brain tumor types have distinct molecular profiles and risk factors, and it is possible that GAA may have varying effects on different subtypes.[23]

Furthermore, our analysis was based on European ancestry populations, potentially limiting the generalizability of our findings to other ethnic groups. Epigenetic patterns and their associations with disease risk can vary across populations, underscoring the need for diverse genetic studies.[24] Additionally, while GAA is a comprehensive measure of epigenetic age acceleration, it may not capture all relevant aspects of epigenetic dysregulation in cancer development.

Conclusion

In summary, our MR study does not support a causal association between DNA methylation GrimAge acceleration and brain tumor incidence. While epigenetic processes are central to brain tumor biology, accelerated epigenetic aging as measured by GAA appears unlikely to be a key causal factor. Future research should focus on alternative epigenetic or genetic pathways and subtype-specific investigations in diverse populations.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Affiliated Hospital of Beihua University (20240101). We confirm that our study uses only publicly available, de-identified, summary-level genetic data (GWAS data), informed consent is not required.

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Disclosure

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately for this work.

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