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ORIGINAL ARTICLE

# Hypothyroidism and glioblastoma risk: a two-sample Mendelian randomization study

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## Abstract

**BACKGROUND:** Prior observational evidence suggests a potential link between hypothyroidism and glioblastoma (GBM) risk. To investigate causality, we conducted a two-sample Mendelian randomization (MR) study.

**METHODS:** Between April 2025 and July 2025, we leveraged summary - level data from European - ancestry genome-wide association studies (GWAS). The inverse - variance weighted (IVW) approach served as the primary method for causal inference. Robustness was evaluated using four complementary Mendelian randomization (MR) techniques: MR-Egger techniques: MR-Egger, weighted median (WM), weighted mode, and simple mode. Multiple sensitivity analyses were performed to assess stability, heterogeneity, and potential horizontal pleiotropy.

**RESULTS:** Twenty-nine hypothyroidism-associated single nucleotide polymorphisms (SNPs) were used as instruments. IVW analysis indicated a significant protective effect of hypothyroidism on glioblastoma (GBM) risk (odds ratio, OR = 0.759; 95% confidence interval, CI: 0.606–0.949; $p = 0.016$). Consistent estimates were obtained via MR-Egger (OR = 0.565, $p = 0.032$), weighted median (OR = 0.674, $p = 0.017$), and weighted mode (OR = 0.581, $p = 0.02$). Simple mode was non-significant but directionally consistent. Sensitivity analyses showed no heterogeneity or horizontal pleiotropy.

**CONCLUSION:** Employing Mendelian randomization, this investigation provides preliminary genetic evidence suggesting a potential protective association between hypothyroidism and glioblastoma risk. However, the limited case sample (N = 406) and the hypothesis-generating nature of Mendelian randomization (MR) warrant cautious interpretation and replication in larger cohorts.

**Abbreviations:**

| | |
|---|---|
| GBM | - Glioblastoma |
| GWAS | - Genome-wide association studies |
| IVs | - Instrumental variables |
| IVW | - Inverse-variance weighted |
| LD | - Linkage disequilibrium |
| MR | - Mendelian randomization |
| MR-PRESSO | - MR-PRESSO: Mendelian Randomization Pleiotropy RESidual Sum and Outlier |
| RCTs | - Randomized controlled trials |
| SNPs | - Single nucleotide polymorphisms |
| TSH | - Thyroid-stimulating hormone |
| WHO | - World Health Organization |
| WM | - Weighted median |

## INTRODUCTION

Glioblastoma (GBM), classified by the WHO as grade IV glioma, constitutes the most common and aggressive primary central nervous system tumor (Louis *et al.* 2021; Song *et al.* 2024). Its characteristically rapid proliferation and diffuse invasiveness contribute to exceptionally poor prognoses. Representing nearly half (49%) of malignant intracranial neoplasms (Schaff & Mellinghoff 2023), GBM exhibits an annual incidence of ~3 cases per 100,000 population (Agosti *et al.* 2023). Current first-line management combines maximal safe resection with adjuvant temozolomide-based chemoradiation (Rong *et al.* 2022). Despite these interventions, therapeutic efficacy remains suboptimal—reflected in median survival below 15 months and <10% 5-year survival rates (Venkataramani *et al.* 2022). Well-documented risk factors encompass advanced age, ionizing radiation exposure, and familial glioma predisposition (Aiyappa-Maudsley *et al.* 2022; Bruno *et al.* 2022; Choi *et al.* 2023). Identifying modifiable risk factors and enabling early detection are crucial for developing preventive strategies to improve outcomes and reduce healthcare expenditures.

Hypothyroidism, characterized by elevated thyroid-stimulating hormone (TSH) and low or normal-range thyroid hormone levels, represents the most prevalent autoimmune disorder in adults. Its clinical manifestations, including cold intolerance, fatigue, and constipation, arise from mucopolysaccharide accumulation in skin and connective tissues. Thyroid function exhibits age-dependent decline, showing prevalence escalation from 5.1% among women aged 45–64 years to 12.7% in the ≥65-year cohort (Prados-Torres *et al.* 2018). Emerging evidence indicates a dependency of GBM cells on thyroid hormones (Sudha *et al.* 2017). This clinical evidence parallels *in vitro* findings that thyroid hormones stimulate glioma cell proliferation via integrin αvβ3-mediated activation of the MAPK/ERK signaling pathway (Davis *et al.* 2006). However, a definitive causal link between hypothyroidism and GBM pathogenesis remains elusive. To investigate this putative causal link, we implemented a two-sample Mendelian randomization (MR) framework evaluating hypothyroidism's causal impact on GBM susceptibility.

While epidemiological research evaluates associations between exposures and clinical endpoints, randomized controlled trials (RCTs) remain the benchmark for causal determination. Traditional observational approaches, however, commonly demonstrate susceptibility to unaccounted confounding. MR, initially proposed by Katan (1986) (Emdin *et al.* 2017), utilizes inherited genetic variants (mainly SNPs) as IVs to derive causal estimates between risk factors and outcomes, thereby reducing confounding and reverse causation effects.

MR has found extensive application in investigating causal links involving hypothyroidism and associated genetic factors (Li *et al.* 2024; Zhou *et al.* 2024; Yin *et al.* 2025). Beyond cardiovascular and hematologic traits, thyroid dysfunction has also been evaluated in relation to cancer risk using MR. A two-sample MR study by Yuan *et al.* systematically examined four indicators of thyroid function and dysfunction across 22 site-specific cancers, including brain cancer, and reported a non-significant inverse association between genetically predicted hypothyroidism and brain cancer risk (Yuan *et al.* 2020). However, that analysis was not glioblastoma-specific and relied on relatively few brain cancer cases, leaving the hypothyroidism–GBM relationship unresolved. This study uses two-sample MR to test whether genetically predicted hypothyroidism is causally associated with GBM risk, aiming to inform preventive strategies and clarify the biological pathways linking thyroid function to gliomagenesis.

## MATERIALS AND METHODS

### *Study design*

Employing a two-sample MR design, we examined the causal link between hypothyroidism and GBM susceptibility. Genetic variants meeting instrumental variable (IV) criteria were incorporated, with data sourced from GWAS. The analytical framework is schematized in Fig. 1. Methodological rigor was enhanced through sensitivity evaluations confirming causal directionality and result robustness. This investigation complied with STROBE-MR guidelines for reporting MR studies (Skrivankova *et al.* 2021).

### *Assumptions of the MR analysis*

Validity of Mendelian randomization analysis hinges upon three fundamental principles to mitigate bias. Instrumental variables must demonstrate robust association with the exposure, operationalized through genome-wide significant variants (e.g., $p < 5.0 \times 10^{-8}$ or $p < 5.0 \times 10^{-6}$). Genetic instruments further require independence from confounding factors, achieved via linkage disequilibrium (LD) clumping during selection. Horizontal pleiotropy was assessed via the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) framework, which comprises a global test for overall horizontal pleiotropy, an outlier test for

**Tab. 1.** Summary of the GWAS included in this study

| Traits | GWAS ID | Sample size | Number of variants | Population | Sex | Year |
|---|---|---|---|---|---|---|
| Hypothyroidism | ebi-a-GCST90018862 | 410 141 | 24 138 872 | European | Males and Females | 2021 |
| Glioblastoma | finngen_R12_C3_GBM_EXALLC | 378 749 | 21 325 039 | European | Males and Females | 2024 |

detection of pleiotropic instruments, and a distortion test comparing causal estimates before and after outlier removal, in conjunction with MR-Egger regression (Verbanck *et al.* 2018). Central to MR validity is the requirement that instrumental variables affect outcomes solely through the exposure pathway. This exclusion restriction principle was enforced by removing pleiotropic SNPs identified through PhenoScanner V2 database screening, with nonsignificant MR-Egger intercepts ($p > 0.05$) confirming absence of horizontal pleiotropy. Strict adherence to these principles underpins the reliability of causal inference.

*Data sources for GBM*

Genetic susceptibility data for glioblastoma originated from the FinnGen Consortium R12 repository. We employed publicly accessible genome-wide association study (GWAS) summary statistics comprising 406 histologically confirmed GBM cases and 378,749 malignancy-free controls of European descent. This de-identified dataset, excluding all cancer diagnoses, required no additional ethics review or participant consent. Comprehensive population characteristics and data provenance are detailed in Table. 1.

*Selection of IVs*

IVs were selected from genome-wide significant hypothyroidism-associated SNPs applying stringent criteria: association significance ($p < 5.0 \times 10^{-10}$), LD independence ($r^2 < 0.0001$), and 100,000 kb clumping distance. These genetic instruments originated from a large GWAS meta-analysis of European-ancestry populations (N = 410,141) at the time the analysis plan was finalized (Sakaue *et al.* 2021). A more recent, substantially larger meta-analysis including 113,393 hypothyroidism cases and 1,065,268 controls identified 350 lead variants associated with hypothyroidism, which may enable construction of stronger instruments in future work (Rand *et al.* 2025). Systematic exclusion of SNPs demonstrating residual LD or violating core MR principles guaranteed IV validity. Weak instrument assessment employed the F-statistic ($F = \beta^2$/ ($F = \beta^2$/*standard error, SE*$^2$, where β represents the SNP effect size and SE its standard error in the SNP-hypothyroidism association) (Pierce *et al.* 2011), with all selected instruments exceeding the empirically established threshold (F > 10), effectively eliminating weak instrument concerns.

*Two-sample MR analysis*

Causal inference analysis employed two-sample Mendelian randomization implemented via the TwoSampleMR package (R version 4.4.3) to investigate hypothyroidism-GBM relationships. Primary causal estimates derived from IVW regression, supplemented by four complementary approaches: MR-Egger regression, WM, simple mode, and weighted mode estimators. The IVW method provides unbiased effect estimates when pleiotropic effects balance across instrumental variables (Burgess *et al.* 2017). WM estimation remains valid when ≥50% of instruments satisfy core

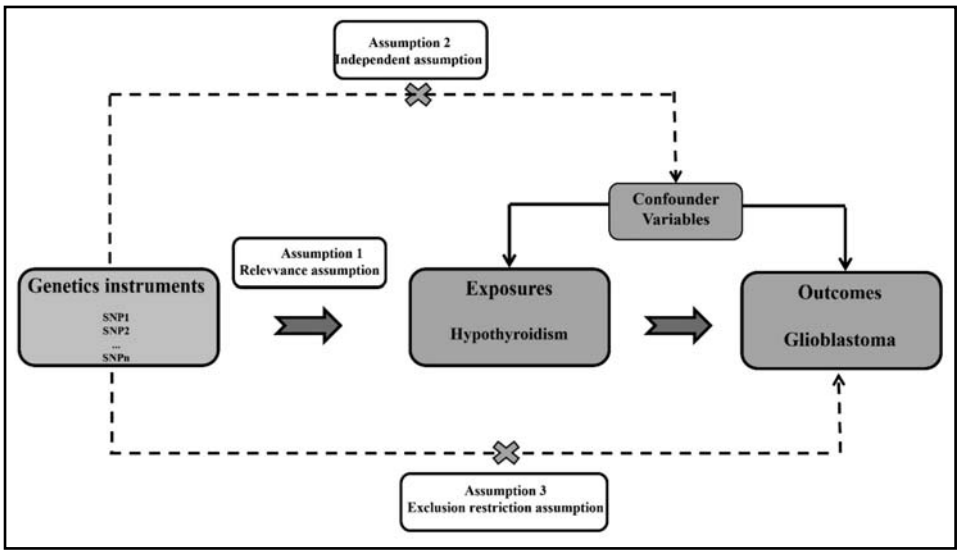


**Fig. 1. Schematic of the Mendelian Randomization (MR) Study Design.**
The directed acyclic graph illustrates the causal investigation between hypothyroidism (exposure) and glioblastoma (GBM; outcome). The model assumes the 29 selected genetic variants (instrumental variables, IVs) satisfy three core assumptions: (1) robust association with hypothyroidism; (2) independence from confounders; and (3) effect on GBM mediated solely through the thyroid pathway (no horizontal pleiotropy).

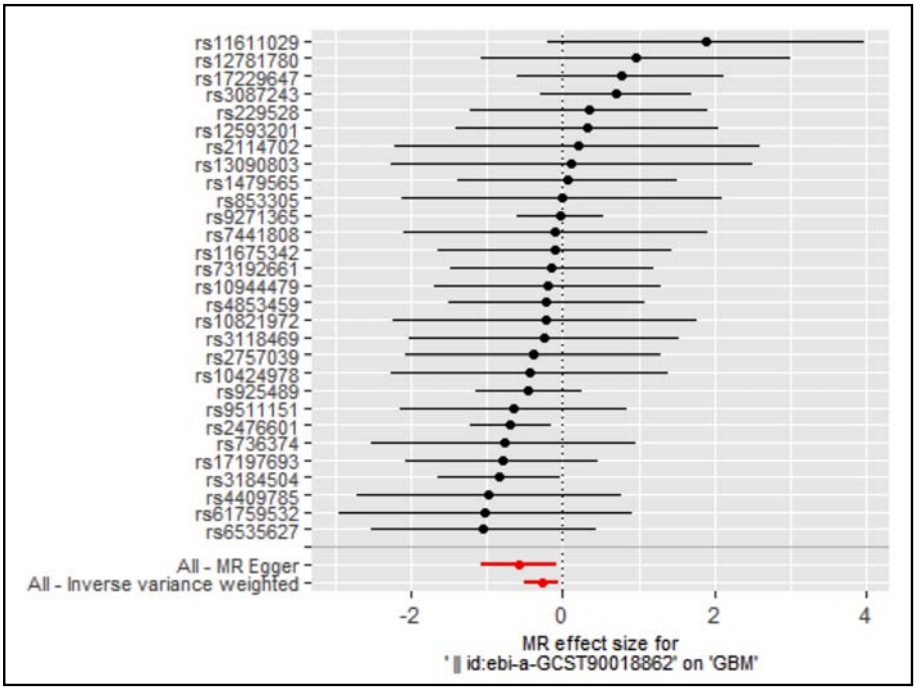


**Fig. 2. Forest plot of causal effects.** Black points represent the causal effect estimate (log odds ratio) for each of the 29 hypothyroidism-associated single nucleotide polymorphisms (SNPs) on glioblastoma (GBM) risk. Horizontal lines indicate the 95% confidence intervals (CIs). The red lines at the bottom display the combined causal estimates calculated using inverse-variance weighted (IVW), Mendelian randomization Egger regression (MR-Egger), weighted median (WM), weighted mode, and simple mode methods.

assumptions (Bowden *et al.* 2016), while MR-Egger regression incorporates directional pleiotropy adjustment through its intercept parameter, enabling robust inference even with widespread invalid instruments (Bowden *et al.* 2015).

*Sensitivity analysis*

Methodological robustness was assessed through comprehensive sensitivity analyses. Instrument heterogeneity quantification employed Cochran's *Q* statistic from inverse-variance weighted regression (Yang *et al.* 2023). Horizontal pleiotropy evaluation utilized MR-Egger intercept testing with statistical significance thresholded at $\alpha = 0.05$ (Qi *et al.* 2023). Implementation of leave-one-out validation and MR-pleiotropy residual sum and outlier (MR-PRESSO) methodologies identified influential SNPs potentially biasing causal estimates (Xu & Wang 2023). All analytical workflows were performed in R using the TwoSampleMR package, ensuring methodological consistency throughout.

*Ethics statement*

Analyses exclusively utilized publicly available summary data from prior studies. Consequently, formal ethics committee review and individual participant consent were waived for this investigation.

## RESULTS

Following rigorous quality control procedures, 29 hypothyroidism-associated SNPs were retained as IVs from the GWAS with F-statistics >10. Post hoc power analysis ($\alpha = 0.05$, N = 406 cases, OR = 0.759) yielded 82% power for the primary IVW effect; smaller effects (OR $\geq 0.85$) had <50% power. Causal inference robustness was further confirmed through two-sample Mendelian randomization analysis. Directional effects of individual SNP loci on GBM pathogenesis were systematically quantified, with comprehensive results visualized in Fig. 2.

**Tab. 2.** The MR estimates from each method of assessing the causal effect of hypothyroidism on the risk of GBM.

| MR method | Number of SNPs | Beta | SE | Association *p* value | Heterogeneity *p* value | Cochran Q statistic | OR | 95% confidence interval |
|---|---|---|---|---|---|---|---|---|
| IVW | 29 | -0.276 | 0.114 | 0.016 | 0.792 | 21.763 | 0.759 | 0.606-0.949 |
| Weighted median | 29 | -0.394 | 0.165 | 0.017 | - | - | 0.674 | 0.488-0.932 |
| Weighted mode | 29 | -0.544 | 0.221 | 0.021 | - | - | 0.581 | 0.376-0.896 |
| Simple mode | 29 | -0.162 | 0.331 | 0.628 | - | - | 0.851 | 0.444-1.627 |
| MR-Egger | 29 | -0.572 | 0.252 | 0.032 | 0.829 | 20.033 | 0.565 | 0.344-0.925 |

Beta, β coefficient; MR, Mendelian randomization; SE, standard error; SNPs, single nucleotide polymorphisms.

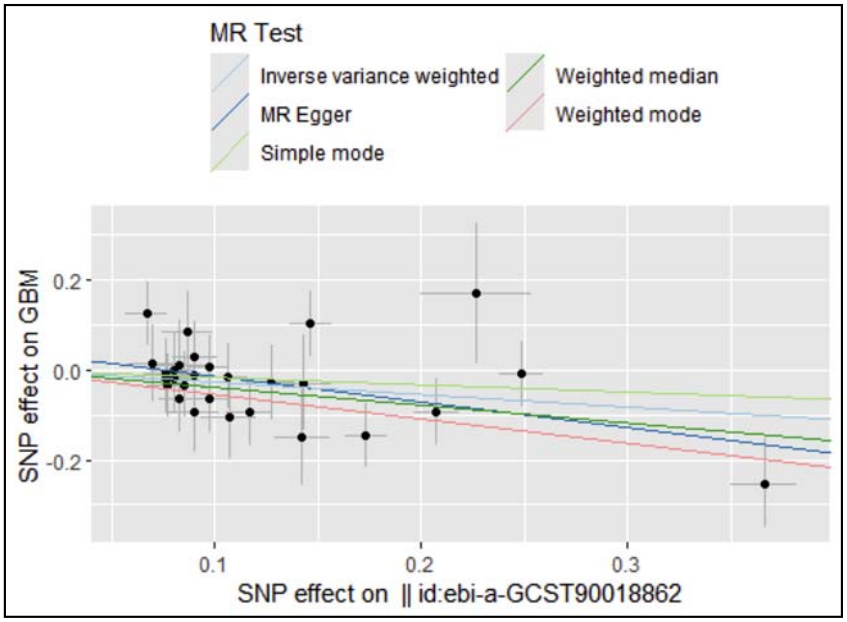


**Fig. 3. Scatter plot of genetic associations.** The x-axis represents the genetic association with hypothyroidism (exposure), and the y-axis represents the genetic association with glioblastoma (GBM; outcome) for each single nucleotide polymorphism (SNP). The colored regression lines correspond to different Mendelian randomization (MR) methods; the slope of each line represents the estimated causal effect. The consistent negative slopes visually confirm the protective association

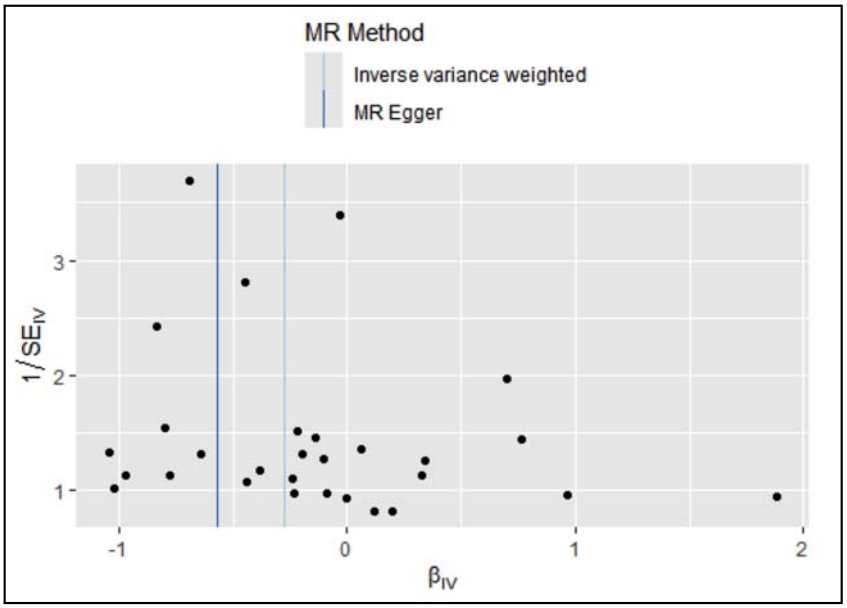


**Fig. 4. Funnel plot for assessment of pleiotropy.** Individual causal effect estimates (x-axis) are plotted against their instrumental precision (1/standard error, SE; y-axis). The symmetry of the distribution around the vertical inverse-variance weighted (IVW) estimate line indicates an absence of significant directional horizontal pleiotropy or small-study bias.

The IVW method revealed an protective association between genetically predicted hypothyroidism and GBM risk (odds ratio, OR = 0.759; 95% confidence interval, CI: 0.606–0.949; $p = 0.016$), indicating protective association against GBM development. MR-Egger regression corroborated this protective relationship (OR = 0.565, 95% CI: 0.344–0.925, $p = 0.032$), with the exclusion of the null value (OR = 1) from the confidence interval confirming statistical significance. WM analysis demonstrated comparable protective association (OR = 0.674, 95% CI: 0.488–0.932, $p = 0.017$), while weighted mode estimation yielded more pronounced effects (OR = 0.581, 95% CI: 0.376–0.896, $p = 0.020$). Although simple mode analysis followed a similar directional trend (OR = 0.851, 95% CI: 0.444–1.627), the association lacked statistical significance ($p = 0.628$) due to CI overlap with the null hypothesis value (Table 2, Fig. 3).

MR-Egger regression showed no significant evidence of directional pleiotropy (intercept $p = 0.199$), though this test has limited power with 29 instruments, with funnel plot symmetry corroborating the absence of systematic heterogeneity across instrumental variants (Fig. 4).

Heterogeneity - defined as either variability in causal effect estimates across individual SNPs or inconsistency in pooled causal estimates – was rigorously assessed in this investigation. Cochran's $Q$ test revealed no significant heterogeneity among instrumental variable estimates, confirming consistency across genetic instruments. Leave-one-out sensitivity analysis further demonstrated that no single SNP disproportionately influenced the IVW point estimate, with sequential

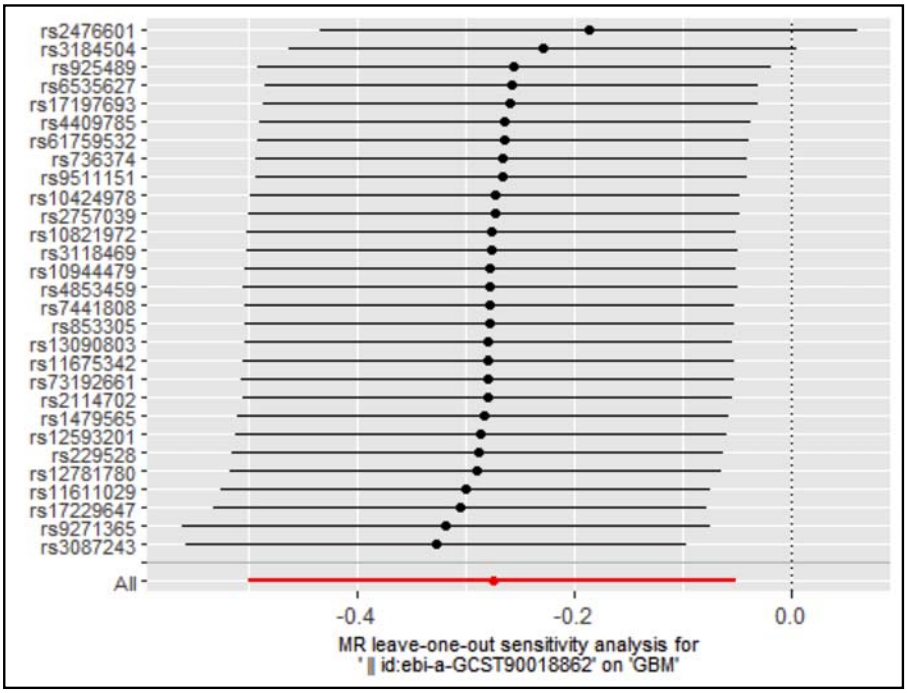


**Fig. 5. Leave-One-Out Sensitivity Analysis.**
Each black point represents the recalculated inverse-variance weighted (IVW) causal estimate (odds ratio, OR) after sequentially excluding one single nucleotide polymorphism (SNP). The error bars indicate 95% confidence intervals (CIs). The stability of the estimates (all remaining < 1.0 and on the same side of the null) confirms that the protective association is robust and not driven by any single influential outlier.

exclusion of individual variants producing stable effect sizes within narrow confidence intervals (Fig. 5). These complementary analyses substantiate the robustness and reliability of the primary causal inference.

Complementary assessment using the MR-PRESSO global test did not detect significant evidence of horizontal pleiotropy (global test $p > 0.05$). No outlier instruments were identified, so distortion testing was not required. These findings are consistent with the absence of heterogeneity from Cochran's $Q$ test and the null MR-Egger intercept, collectively supporting the validity of the causal estimates under the core MR assumptions (Verbanck *et al.* 2018).

While funnel plot asymmetry could theoretically indicate directional pleiotropy – a critical confounding factor in MR analyses – both MR-Egger regression (intercept $p = 0.199$) and quantitative funnel plot evaluation demonstrated symmetrical distribution of effect estimates across genetic instruments. Complementary assessment through Cochran's $Q$ statistic confirmed homogeneity of causal effects, with visual inspection of funnel plot symmetry reinforcing the absence of systematic bias. This concordance across multiple analytical frameworks substantiates the validity of causal inferences by effectively excluding significant horizontal pleiotropy as a source of estimation bias.

## DISCUSSION

Our two-sample MR analysis suggests that genetically predicted hypothyroidism is associated with reduced GBM risk, complementing experimental evidence of thyroid hormone-mediated tumor promotion. By employing genetic variants as IVs, this approach reduces susceptibility to residual confounding and reverse causality inherent in observational studies (Emdin *et al.* 2017; Skrivankova *et al.* 2021). However, the limited case sample (N = 406), modest statistical significance (IVW $p = 0.016$), and absence of bidirectional MR analysis mean these findings should be interpreted as hypothesis-generating evidence of a potential protective association, rather than confirmation of a causal relationship. These findings are directionally consistent with prior MR work on thyroid dysfunction and site-specific cancers. Yuan *et al.* conducted a large two-sample MR study of four thyroid function indicators across 22 cancer types and observed a non-significant trend toward reduced brain cancer risk among individuals genetically predisposed to hypothyroidism, alongside a positive association between hyperthyroidism and brain cancer risk (Yuan *et al.* 2020). Importantly, their analysis did not isolate glioblastoma and included a limited number of brain cancer cases, whereas the present study focuses specifically on GBM, using 406 histologically confirmed cases from FinnGen. Taken together, the suggestive causal protective effect of hypothyroidism and positive association of hyperthyroidism with brain cancer in Yuan *et al.* and the GBM-specific protective association observed here support a biologically coherent model in which higher thyroid hormone activity promotes gliomagenesis, whereas reduced thyroid function may confer relative protection.

These findings align with preclinical models demonstrating pro-tumorigenic effects of thyroid hormone signaling. L-thyroxine (T4) stimulates proliferation in GL261 murine and C6/F98 rat glioma cell lines (Davis *et al.* 2006), while pharmacologically induced hypothyroidism inhibits tumor progression in rodent GBM models (Sudha *et al.* 2017).

Mechanistically, thyroid hormones bind integrin αVβ3 – a key mediator of MAPK activation, growth factor signaling, and angiogenesis. The primary IVW estimate (OR = 0.759) suggests a 24% suggestive causal protective effect per genetically determined unit increase in hypothyroidism liability. Four of five MR methods yielded directionally consistent suggestive causal protective effect (OR range: 0.565–0.759), though the wide effect-size range and the non-significant simple mode result (OR = 0.851, $p$ = 0.628) indicate residual uncertainty. Given the limited case sample (N = 406), these estimates should be interpreted as hypothesis-generating rather than definitive. This interaction mirrors the antitumor activity of tetraiodothyroacetic acid and aligns with clinical observations that propylthiouracil-induced hypothyroidism extended survival in compassionate-use GBM patients (Hercbergs *et al.* 2003, 2015) – potentially via blockade of thyroid hormone binding to integrin αVβ3 – suggesting that pharmacological modulation of thyroid signaling warrants prospective evaluation. Thyroid hormone deprivation upregulates p21 cyclin-dependent kinase inhibitor via p53-independent pathways, inducing cell cycle arrest in astrocytoma models (Toms *et al.* 1998). Concurrent tumor microenvironment modulation through altered immune cell function and cytokine secretion (Moeller & Führer 2013) may create an inhospitable niche for glioma proliferation, though precise mechanisms require elucidation.

However, critical questions remain regarding whether hypothyroidism directly inhibits tumor growth or merely reflects treatment-related metabolic changes—a distinction with profound clinical implications for developing transient therapeutic interventions without inducing chronic hypothyroidism.

This integrative analysis extends previous research on GBM's thyroid hormone dependency through concordant genetic epidemiological, preclinical, and clinical evidence. MR serves as a hypothesis-generating tool; these findings suggest but do not prove a causal link, and replication in larger cohorts and prospective clinical studies is needed before therapeutic implications can be drawn.

Five key limitations warrant consideration. First, the case sample (N = 406) achieved 82% power for the observed effect (OR = 0.759) but limits detection of weak genetic associations (OR ≥ 0.85: <50% power). Replication in larger GBM cohorts (≥1,000 cases) is essential. Second, the reliance on lifetime genetic risk exposure obscures critical temporal dynamics in hormone-cancer interactions, as the timing of thyroid hormone dysregulation (e.g., early adulthood versus later life) may differentially impact GBM development. Third, European ancestry predominance in existing studies limits generalizability across diverse populations, as genetic architectures, hormone metabolism, and cancer susceptibility can vary substantially by ethnic group. Fourth, the absence of molecular subtype stratification—particularly regarding IDH-mutant versus wild-type tumors - in current GWAS data hinders pathway-specific analyses, as distinct GBM subtypes may exhibit divergent responses to thyroid hormone signaling. Fifth, our instruments were derived from an earlier hypothyroidism GWAS (N = 410,141), whereas a subsequent meta-analysis including 113,393 cases and 1,065,268 controls identified 350 lead variants and more completely characterized the genetic architecture of hypothyroidism (Rand *et al.* 2025). Although our F-statistics exceeded 10, future MR studies integrating these newer variants may achieve greater instrument strength and precision in estimating the hypothyroidism–GBM association. These limitations should be acknowledged when interpreting the study results and guiding future research directions.

Future investigations should prioritize integrating age-stratified genetic data with multi-omics approaches to delineate thyroid hormone-regulated transcriptomic and epigenomic signatures in glioma stem cells (Moeller & Führer 2013). Prospective clinical trials evaluating pharmacological modulation of thyroid hormone signaling in neuro-oncology are needed to determine if targeting downstream pathways (e.g., integrin αvβ3) improves therapeutic outcomes, mimicking the protective metabolic state without inducing systemic endocrine dysfunction (Hercbergs *et al.* 2015). Such studies must address critical questions: Which molecular subtypes of glioma demonstrate greatest responsiveness to thyroid hormone depletion? Can transient hormonal modulation achieve antitumor effects without causing irreversible endocrine disruption? Mechanistic studies should further clarify whether thyroid hormone deprivation exerts direct cytotoxic effects or acts indirectly through tumor microenvironment remodeling (Toms *et al.* 1998).

## CONCLUSION

This MR analysis provides preliminary genetic evidence for a protective association between genetically predicted hypothyroidism and GBM risk. While four of five MR methods yielded consistent inverse associations and sensitivity analyses detected no significant pleiotropy, the limited case sample (N = 406) and modest statistical significance (IVW $p$ = 0.016) necessitate replication before clinical implications can be considered. To strengthen causal inference and clinical generalizability, future investigations should prioritize multi-ethnic cohort recruitment to address population-specific genetic architectures, complemented by expanded sample sizes for enhanced statistical power. Furthermore, functional characterization of identified SNPs and multi-omics integration should be pursued to elucidate biological mechanisms underlying thyroid-GBM axis regulation. Such coordinated efforts may ultimately advance personalized prevention strate-

gies targeting downstream endocrine pathways (e.g., integrin αvβ3) in neuro-oncology.

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**Conflict of interest:** The authors affirm the absence of any commercial affiliations or financial involvements constituting potential conflicts of interest.

**Data Availability:** All analyses used publicly available GWAS summary statistics. Exposure data are available from the GWAS Catalog (ebi-a-GCST90018862), and outcome data from FinnGen R12 (finngen_R12_C3_GBM_EXALLC). The instrument list and analysis code are available from the corresponding author upon reasonable request.

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