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Genetic association of type 2 diabetes mellitus and glycaemic factors with primary tumours of the central nervous system

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Abstract

Type 2 diabetes mellitus (T2DM) is a pivotal chronic disease with an increasing prevalence. Recent studies have found associations between T2DM and the development of central nervous system (CNS) tumours, a special class of solid tumours with an unclear pathogenesis. In this study, we aimed to explore the relationship between T2DM and certain glycaemic factors with common CNS tumours by using genetic data to conduct Mendelian randomization (MR) and co-localisation analysis. We found a causal relationship between T2DM and glioblastoma, fasting glucose and spinal cord tumours, glycated haemoglobin and spinal cord tumours, and insulin-like growth factor-1 and spinal cord tumours, pituitary tumours, and craniopharyngiomas. These results clarify the relationship between T2DM, glucose-related factors, and common CNS tumours, and they provide valuable insight into further clinical and basic research on CNS tumours, as well as new ideas for their diagnosis and treatment.

Keywords Type 2 diabetes mellitus, Fasting glucose, Fasting insulin, Insulin-like growth factor-1, Glycated haemoglobin, Central nervous system tumours

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterised by impaired blood glucose regulation [1] and systemic complications [2]. In recent years, the incidence of T2DM has gradually increased [3], affecting not only middle-aged and older people but also young children [4–6]. The primary concern with T2DM is its complications [7], particularly cardiovascular disease, which is the leading cause of death in affected patients [8]. Current treatments for T2DM include lifestyle modifications and pharmacological therapies [1, 9, 10], which can manage but not cure the condition. Previous studies have found that T2DM is associated with genetic and non-genetic factors, such as lifestyle and stress [11, 12]. It is also associated with various diseases, such as non-alcoholic fatty liver disease [13], inflammatory bowel disease [14], and schizophrenia [15].

Central nervous system (CNS) tumours are a group of tumours originating from cells within or around the brain, including primary and metastatic tumours. These tumours have very high morbidity and mortality rates [16] and affect both adults and children; they are a leading cause of death in affected children [17, 18]. The main treatment modalities for CNS tumours include surgery, radiotherapy, and drug therapy [19]. While benign CNS tumours typically have good results with standard treatment, malignant CNS tumours have a poor prognosis [20, 21]. Previous studies have found links between CNS tumours and factors such as intestinal microbiota [22]

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and obesity [23]; however, these studies were inconclusive. Advances in genomics are gradually uncovering the complexities of CNS tumours [24], leading to some progress in treatment, but substantial breakthroughs are yet to be achieved.

Type 2 diabetes mellitus is associated with a wide range of systemic disorders and has a role in various gastrointestinal diseases [25] and psychiatric disorders [26]. Some studies have also found a link between T2DM and certain CNS tumours. One retrospective study found no association between T2DM and glioblastoma development, but it was found that some association between level of glycaemic control and survival time in glioblastoma patients [27]. Type 2 diabetes and obesity are independent risk factors for the prognosis of high-grade gliomas [28]. However, the roles of T2DM and glucose-related factors in the development of glioblastomas remain understudied.

A previous study reported a negative correlation between T2DM and meningiomas [29], particularly in female patients. A retrospective study identified T2DM as an independent factor affecting the length of postoperative survival in patients with meningiomas [30]; however, the relationship between T2DM and meningiomas has not been extensively studied. Additionally, one study found that a high mortality rate in patients with craniopharyngiomas was associated with T2DM [31], but the cause was not determined.

With continuous progress in genome-wide association studies (GWAS), millions of individual genetic variants have been sequenced [32], providing a valuable resource for conducting genotypic studies. Consequently, MR, a causal inference method using nucleotide polymorphisms as instrumental variables, has emerged. Exploring the relationship between exposure and outcome using MR has the distinct advantage of effectively avoiding interference from confounding factors [33].

Previous observational studies have identified strong associations between T2DM, related glycaemic factors, and CNS tumours [34]. To clarify these relationships, we utilised MR and co-localisation. We examined T2DM, fasting glucose, fasting insulin, glycated haemoglobin, and insulin-like growth factor-1 in relation to six common CNS tumours: glioblastoma, benign meningioma, malignant meningioma, benign cranial nerve tumours, pituitary tumours, craniopharyngiomas, and benign spinal cord tumours. This novel MR study aimed to thoroughly examine the relationship between blood glucose-related factors and primary CNS tumours, providing new insights into the prevention and treatment of common CNS tumours.

Materials and methods

Study design

In this study, we used MR as the primary research method to investigate the causal relationship between T2DM and glucose-related factors in six groups of common CNS tumours. MR is a research method for causal inference that utilises single-nucleotide polymorphisms (SNPs) as instrumental variables [35]. The selection of the instrumental variable must satisfy three conditions: first, the instrumental variable must be significantly correlated with the exposure; second, the instrumental variable must affect the outcome solely through the exposure, not through other pathways; and third, the instrumental variable must not be confounded by other factors [36]. We then conducted co-localisation analyses to explore common genetic correlation loci between exposure and outcome to verify the causality [37]. No ethical approval was required for this study because all data were derived from secondary analyses of publicly available gene sequencing data and did not contain information about any individuals. In addition, our manuscripts comply with STROBE-MR guidelines.

Exposure data

Datasets on blood glucose-related factors levels were retrieved from the GWAS. These comprised five datasets: T2DM (ebi-a-GCST006867), fasting insulin (ebi-a-GCST90002238), fasting glucose (ebi-a-GCST90002232), glycated haemoglobin (ebi-a-GCST90014006), and insulin-like growth factor-1 (ebi-a-GCST90014008). All datasets for the exposure were derived from the European Individuals Study.

The T2DM dataset included 62,892 European individuals with 655,6666 samples and 503,070,727 SNPs. The fasting insulin dataset contained 151,0103 samples and 296,64438 SNPs. The fasting glucose dataset included 200,622 samples and 31,008,728 SNPs. The glycated haemoglobin dataset included 389,889 samples and 10,783,722 SNPs. The dataset for insulin like growth factor-1 dataset included 387,834 samples and 10,783,705 SNPs.

Outcome data

We selected six common CNS tumours: glioblastoma (finn-b-C3_GBM), benign meningioma (finn-b-CD2_BENIGN_MENINGES), malignant meningioma (finn-b-C3_MENINGES), pituitary and craniopharyngioma (finn-b-C3_GBM), cranial nerve tumours (finn-b-C3_GBM), and spinal cord tumours (finn-b-CD2_BENIGN_SPINAL_CORD). We obtained the data for these tumour types from the Finngen database, which contains a rich dataset of genetic loci [38]. All datasets for the outcome were from European populations. The glioblastoma dataset (n=91) contained 16,380,466 SNPs. The benign

meningioma dataset (n=1280) contained 16,380,466 SNPs. The dataset for malignant meningiomas (n=640) contained 16,380,466 SNPs. The dataset for pituitary tumours and craniopharyngiomas (n=735) contained 16,380,466 SNPs. The dataset for cranial nerve tumours (n=357) contained 16,380,466 SNPs. The dataset for spinal cord tumours (n=196) contained 16,380,466 SNPs.

Instrumental variable selection

To more precisely explore the relationship between blood glucose factors and common CNS tumours, we selected SNP strictly based on $P<5*10^{-8}$ [39]. Considering that a chain imbalance could affect our findings [40], we controlled the clump in the MR process at $r^2=0.001$ and kb=10,000. We selected SNPs that met the above requirements, and to ensure the precision of our findings, we also eliminated palindromic sequences and ambiguous or duplicated SNPs [41]. To ensure a strong correlation in our selected SNPs, we calculated the F-value for each SNP, requiring it to be >10 to ensure the validity of our results [42]. Then, SNPs with F-values<10 were deleted to avoid weakening the reliability of our results. Finally, each SNP was tested using PhenoScanner to exclude the influence of confounding factors.

MR analysis

To study the causal relationship between T2DM, glucose-related factors (fasting insulin, fasting glucose, glycated haemoglobin, and insulin-like growth factor-1), and six common CNS tumours, we utilised four methods: inverse-variance weighted (IVW), MR-Egger (MR-Egger), weighted median (WM), and weighted mode. We used the IVW method as the primary method because of its efficiency in handling instrumental variables in the presence of multiple variants to obtain the most accurate results, as well as its ability to assess the heterogeneity of the results [43]. The remaining three methods were used as supplementary sources of data. The MR-Egger method improves the robustness of results in the presence of null instrumental variables [44], while the WM method remains applicable even in the presence of up to 50% invalid instruments [45], making it a good supplement.

To ensure the reliability of our results, we performed tests of heterogeneity and horizontal multiplicity. For the heterogeneity test, we used Cochran's Q-test based on the IVW and MR-Egger methods, as it showed unique accuracy in the heterogeneity test of pooled data [46]. For the horizontal multivariate validity test, we used the MR-Egger intercept and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) methods. An MR-Egger intercept close to zero indicates minimal horizontal pleiotropy [44]. The MR-PRESSO method, on the other hand, allows for a global test and correction by excluding outliers [47]. We also removed SNPs individually and analysed the effect on the overall results.

Co-localisation analysis

To determine covariation between exposure and outcome, we performed a co-localisation analysis between T2DM and the six common CNS tumours. The co-localisation analysis was based on five hypotheses: H0, no association with any trait; H1, association with trait 1 but not trait 2; H2, association with trait 2 but not trait 1; H3, association with traits 1 and 2, but an independent SNP; and H4, association with traits 1 and 2 in the presence of a common region [48]. During the tests, we referred to the pH4 value, considering a pH4 value>0.8 as indicative of shared causal variance between exposure and outcome. All analyses were conducted using R software version 4.3.2. The packages "TwoSampleMR", "phenoscanner", "MRPRESSO", "LDlink"and "coloc".

Results

MR analysis

Instrumental variable selection

We extracted 114, 38, 63, 352, and 383 SNPs from T2DM, fasting insulin, fasting glucose, glycated haemoglobin, and insulin-like growth factor-1, respectively, at $P<5*10^{-8}$. The F-values for these SNPs met our requirements, and each number of SNPs selected was sufficiently high to ensure robust results.

Causal relationship between glycaemic correlates and glioblastomas

We found that T2DM increased the risk of glioblastoma (OR, 1.600; 95% CI, 1.009–2.536; P=0.046). However, no significant causal relationships were observed for fasting insulin (OR, 6.246; 95% CI,0.194–201; P=0.301), fasting glucose (OR, 3.735; 95% CI,0.589–23.707; P=0.162), glycated haemoglobin (OR, 1.590; 95% CI, 0.749–3.187; P=0.191), and insulin-like growth factor-1 (OR, 0.907; 95% CI, 0.438–1.878; P=0.792) with glioblastomas (Table 1; Fig. 1).

Causal relationship between blood glucose-related factors and benign meningiomas

We found that insulin-like growth factor-1 reduced the risk of benign meningiomas (OR, 0.799; 95% CI, 0.651–0.980; P=0.031). No significant causal relationships were observed for T2DM (OR, 0.944; 95% CI,0.828–1.076; P=0.388), fasting insulin (OR, 0.624; 95% CI, 0.199–1.962; P=0.420), fasting glucose (OR, 0.816; 95% CI, 0.473–1.407; P=0.464), and glycated haemoglobin (OR, 0.957; 95% CI, 0.793–1.154; P=0.643) with benign meningiomas (Table 1; Fig. 1).

Table 1 MR analysis between type 2 diabetes mellitus and glycaemic factors with central nervous system tumours (IVW, inverse-variance weighted mode; SNP, single-nucleotide polymorphisms; HbA1c, glycated haemoglobin; IGF-1, insulin-like growth factor-1)

Exposure	Outcome	Method	nSNP	*P*	OR (95% CI)
Type 2 diabetes	Glioblastoma	IVW	114	0.046	1.600(1.009–2.536)
Fasting insulin	Glioblastoma	IVW	38	0.301	6.246(0.194–201)
Fasting glucose	Glioblastoma	IVW	64	0.162	3.735(0.589–23.707)
HbA1c	Glioblastoma	IVW	352	0.191	1.590(0.794–3.187)
IGF-1	Glioblastoma	IVW	383	0.792	0.907 (0.438–1.878)
Type 2 diabetes	Benign meningioma	IVW	108	0.388	0.944 (0.828–1.076)
Fasting insulin	Benign meningioma	IVW	38	0.42	0.624 (0.199–1.962)
Fasting glucose	Benign meningioma	IVW	64	0.464	0.816 (0.473–1.407)
HbA1c	Benign meningioma	IVW	352	0.643	0.957 (0.793–1.154)
IGF-1	Benign meningioma	IVW	382	0.031	0.799 (0.651–0.980)
Type 2 diabetes	Malignant meningioma	IVW	108	0.107	0.862 (0.720–1.032)
Fasting insulin	Malignant meningioma	IVW	35	0.618	0.701 (0.174–2.830)
Fasting glucose	Malignant meningioma	IVW	64	0.172	0.615 (0.306–1.236)
HbA1c	Malignant meningioma	IVW	352	0.417	0.897 (0.689–1.167)
IGF-1	Malignant meningioma	IVW	383	0.298	0.856 (0.640–1.147)
Type 2 diabetes	Pituitary tumour Craniopharyngioma	IVW	108	0.495	1.056 (0.902–1.237)
Fasting insulin	Pituitary tumour Craniopharyngioma	IVW	38	0.571	0.702 (0.206–2.390)
Fasting glucose	Pituitary tumour Craniopharyngioma	IVW	64	0.849	0.934 (0.464–1.880)
HbA1c	Pituitary tumour Craniopharyngioma	IVW	352	0.327	0.880 (0.682–1.136)
IGF-1	Pituitary tumour Craniopharyngioma	IVW	383	0.006	1.442 (1.108–1.876)
Type 2 diabetes	Cranial neuroma	IVW	108	0.884	1.017 (0.807–1.282)
Fasting insulin	Cranial neuroma	IVW	38	0.303	0.397 (0.069–2.303)
Fasting glucose	Cranial neuroma	IVW	64	0.251	0.552 (0.201–1.521)
HbA1c	Cranial neuroma	IVW	308	0.724	1.076 (0.717–1.615)
IGF-1	Cranial neuroma	IVW	383	0.687	0.924 (0.629–1.357)
Type 2 diabetes	Spinal cord tumour	IVW	108	0.384	1.148 (0.841–1.567)
Fasting insulin	Spinal cord tumour	IVW	38	0.324	0.302 (0.028–3.254)
Fasting glucose	Spinal cord tumour	IVW	63	0.035	4.971 (1.115–22.166)
HbA1c	Spinal cord tumour	IVW	352	0.033	1.692 (1.043–2.743)
IGF-1	Spinal cord tumour	IVW	383	0.218	0.730 (0.442–1.205)

Causal relationship between blood glucose-related factors and malignant meningiomas

We found no significant causal relationships between malignant meningiomas and T2DM (OR, 0.862; 95% CI, 0.720–1.032; P=0.107), fasting insulin (OR, 0.701; 95% CI, 0.174–2.830; P=0.618), fasting glucose (OR, 0.615; 95% CI, 0.306–1.236; P=0.172), glycated haemoglobin (OR, 0.897; 95% CI, 0.689–1.167; P=0.417), and insulin-like growth factor-1 (OR, 0.856; 95% CI, 0.640–1.147; P=0.298) (Table 1; Fig. 1).

Causal relationship between glycaemic correlates and pituitary tumours and craniopharyngiomas

Insulin-like growth factor-1 increased the risk of pituitary tumours and craniopharyngiomas (OR, 1.442; 95% CI, 1.108–1.876; P=0.006). No significant causal relationships were found for T2DM (OR, 1.056; 95% CI, 0.902–1.237; P=0.495), fasting insulin (OR, 0.702; 95% CI, 0.206–2.390; P=0.571), fasting glucose (OR, 0.934; 95% CI, 0.464–1.880; P=0.849), and glycated haemoglobin (OR, 0.880; 95% CI, 0.682–1.136; P=0.327) (Table 1; Fig. 1).

Causal relationship between blood glucose-related factors and pituitary and benign spinal cord tumours

We found that fasting glucose (OR, 4.971; 95% CI, 1.115–22.166; P=0.035) and glycated haemoglobin (OR, 1.692; 95% CI, 1.043–2.743; P=0.333) levels increased the risk of spinal cord tumours. No significant causal relationships were found for T2DM (OR, 1.148; 95% CI, 0.841–1.567; P=0.384), fasting insulin (OR, 0.302; 95% CI, 0.028–3.254; P=0.324), and insulin-like growth factor-1 (OR, 0.730; 95% CI, 0.442–1.205; P=0.218) with benign spinal cord tumours (Table 1; Fig. 1).

Causal relationship between blood glucose-related factors and pituitary and benign cranial nerve tumours

We found no significant causal relationships between benign cranial nerve tumours and T2DM (OR, 1.017; 95% CI, 0.807–1.282; P=0.884), fasting insulin (OR, 0.397; 95% CI, 0.069–2.303; P=0.303), fasting glucose

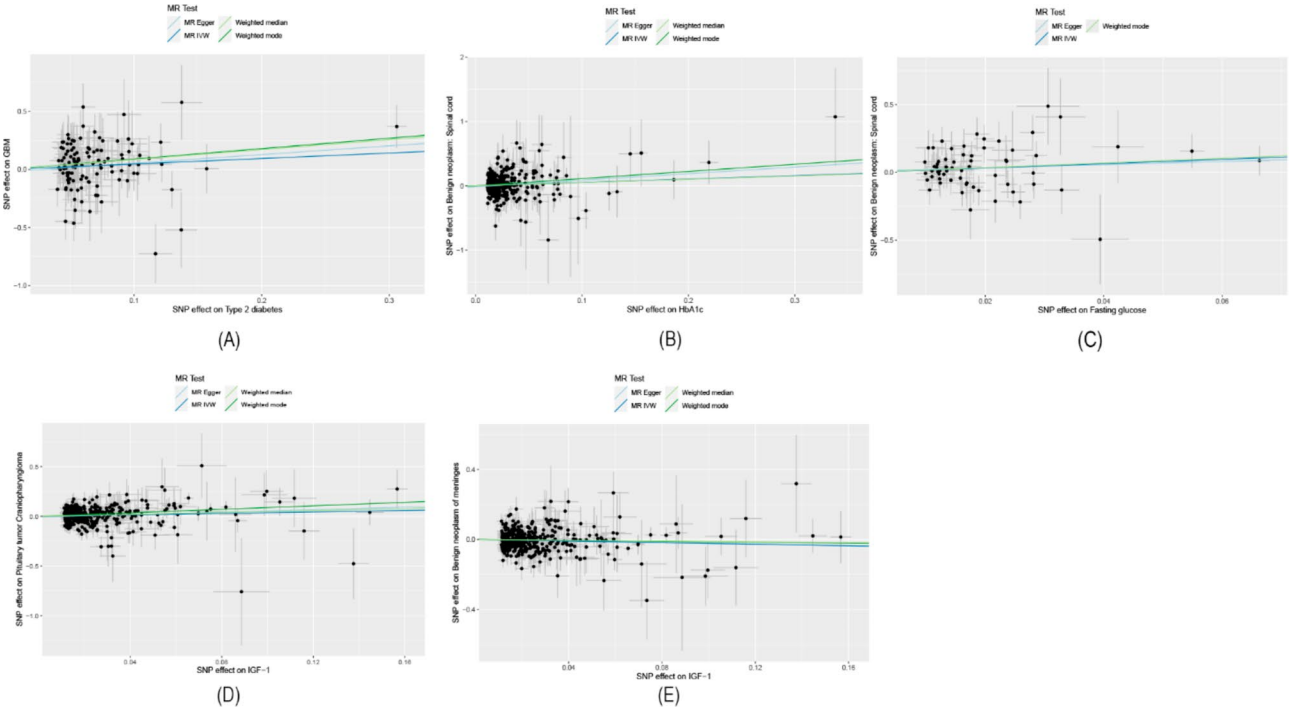

Fig. 1 Scatter plots: (**A**) Type 2 diabetes and glioblastoma; (**B**) HbA1c and spinal cord tumour; (**C**) Fasting glucose and spinal cord tumour; (**D**) IGF-1 and pituitary tumour craniopharyngioma; (**E**) IGF-1 and benign meningioma (MR = Mendelian Randomization; HbA1c = glycated haemoglobin; IGF-1 = insulin-like growth factor-1)

Table 2 Heterogeneity and multiple validity tests and co-localisation analysis (MR-PRESSO, MR Pleiotropy RESidual Sum and Outlier; IGF-1, insulin-like growth factor-1; HbA1c, glycated haemoglobin)

		Heterogeneity test		Pleiotropy test		Co-localization
		Q test		P value		
Exposure	Outcome	IVW	MR-Egger	Egger Intercept	MR-PRESSO	H4
Type 2 diabetes	Glioblastoma	0.208	0.195	0.582	0.187	0.311
IGF-1	Benign meningioma	0.109	0.102	0.996	0.137	0.302
IGF-1	Pituitary tumour Craniopharyngioma	0.202	0.205	0.273	NA	0.315
Fasting glucose	Spinal cord tumour	0.279	0.252	0.754	NA	0.586
HbA1c	Spinal cord tumour	0.317	0.327	0.196	0.245	0.716

(OR, 0.552; 95% CI, 0.201–1.521; P=0.251), glycated haemoglobin (OR, 1.076; 95% CI, 0.717–1.615; P=0.724), and insulin-like growth factor-1 (OR, 0.924; 95% CI, 0.629–1.357; P=0.687) (Table 1; Fig. 1).

Sensitivity analyses

We used Cochran's Q test based on the IVW and MR-Egger methods and found no significant heterogeneity in the results. For the horizontal pleiotropy test, the MR-Egger intercept and MR-PRESSO methods indicated no significant pleiotropy in the results (Table 2). In the leave-one-out analysis, no individual SNP significantly affected the overall validity of the results.

Co-localisation analysis

We performed a co-localisation analysis of T2DM and glucose-related factors in six CNS tumours and found no shared causal variants (Table 2). This reinforces the robustness of our results.

Discussion

This study comprehensively investigated the causal relationship between T2DM, related glycaemic factors, and common CNS tumours based on publicly available data. To the best of our knowledge, this is the first MR study to comprehensively investigate the genetic associations between glycaemic factors and six types of common CNS tumours. We also performed co-localisation analyses to search for potential common genetic loci.

Blood glucose is one of the most essential substances for environmental homeostasis in the human body and is especially prone to change, Fluctuations in blood glucose have been associated with a variety of diseases [49]. Type 2 diabetes, a systemic disease characterised by

impaired glucose regulation, is being increasingly studied [50]. In the present study, we found a causal relationship between genetic susceptibility to T2DM and related glycaemic factors and some CNS tumours, suggesting they influence the development of CNS tumours. These findings may advance the study of the pathogenic factors and pathogenesis of CNS tumours, provide new ideas for prevention and management, and advance the development of clinical treatments.

In our study, we found that T2DM increases the risk of glioblastoma. Type 2 diabetes mellitus accounts for more than 90% of diabetes mellitus cases, and genetic factors have been increasingly linked to it [51]. Our study presents different results from those of a previous cross-sectional case-control study [27], in which we found evidence at the genetic level that T2DM increased the risk of glioblastoma. This discrepancy may be due to the interference of multiple factors in their retrospective study, including the level of diabetes control and environmental influences on gene expression. Previous studies have found that higher fetuin-A levels increase the risk of developing T2DM, and aggressive glioblastomas are malignant tumours that ectopically secrete fetuin-A, which may act as a ligand for TLR4 to promote tumourigenesis and progression [52]. Fetuin-A may be a mediator of T2DM with glioblastoma. Surprisingly, existing studies have found that various glucose-lowering drugs inhibit glioblastoma, which undoubtedly provides a new direction for studies exploring the relationship between T2DM and glioblastoma. One study found that metformin prolonged the recurrence time in patients with glioblastoma when used in the treatment of T2DM [53]. The mechanism by which metformin simultaneously treats T2DM and glioblastoma may involve its role as a sensitiser for temozolomide or its induction of AMP-activated protein kinase, which directly inhibits tumour cell proliferation and migration and promotes glioblastoma cell apoptosis [54]. Siglitazone has also been found to be therapeutic for glioblastoma in vivo and in vitro animal experiments [55].

Furthermore, we found no causal relationship between T2DM and benign meningiomas, malignant meningiomas, pituitary tumours and craniopharyngiomas, cranial nerve tumours, or spinal cord tumours. Previous studies have reported a relationship between fat accumulation and meningioma development [56]. Some studies have found an association between T2DM and the postoperative prognosis of meningiomas. Type 2 diabetes mellitus, as a metabolic disease, may affect the development of meningiomas by affecting fat composition and content; however, there is no genetic association between the two. Similarly, a cohort study found a significant reduction in the prevalence of meningiomas in patients using metformin to control T2DM [57]. Four genes (MMP12, PLAU, KRT14, and DKK1) have been found to have roles in the pathogenesis of craniopharyngioma and T2DM with an enrichment of several common immune cells [58], possibly mediating a link between the two. Metformin has shown evidence of potential treatment for pituitary tumours alongside T2DM, but the available studies remain imperfect [59]. Acromegaly, often caused by growth hormone-secreting pituitary tumours, is associated with T2DM in terms of pathogenesis [60] and elevates blood glucose, making it more challenging to treat T2DM. This may serve as a bridge linking the two. The glucose-dependent glucagon receptor is involved in a number of pathological processes in T2DM, and abnormal activation of this receptor has been observed in growth hormone pituitary tumours [57]. The expression of P63 of the P53 family has been found to be potentially associated with the development of acoustic neuromas [61], and specific P63 expression was found to be low in type 2 diabetic livers [62], suggesting a negative correlation between the two. Overexpression of tumour necrosis factor-α (TNFα) was found in the spinal cord of monkeys with T2DM in animal studies [63], whereas patients with spinal cord tumours had elevated TNFα concentrations [64], indicating the presence of common inflammatory factors between T2DM and spinal cord tumours, which may act as mediators of the link between the two. However, we did not find a link at the genetic level.

Among the glucose-related factors, we found that insulin-like growth factor-1 decreased the risk of benign meningiomas and increased the risk of pituitary and craniopharyngiomas, while fasting glucose and glycated haemoglobin increased the risk of spinal cord tumours. A key step in the cascade response in glioblastoma is the optimal use of glucose [65]. An association between blood glucose and the prognosis of glioblastoma has been found in large retrospective studies, but unfortunately, not a genetic association. Hyperglycaemia promotes spinal cord injury through the production of inflammatory mediators following ischaemic injury to the spinal cord, and it is possible that hyperglycaemia promotes spinal cord tumourigenesis and progression through these inflammatory mediators [66, 67]. Glycated haemoglobin levels positively correlate with proliferation levels in glioblastoma [68], and glycated haemoglobin levels and meningiomas are potentially correlated [69]. Glycated haemoglobin is commonly used as a measure of systemic chronic blood glucose levels. We only found a causal association between glycated haemoglobin and spinal cord tumours, with a possible temporal effect on other neurological tumours.

Signal transduction involving insulin-like growth factor-1 has an important role in the proliferation and transformation of glioblastoma [70, 71]. However, we found no causal relationship between the two, pointing to a

direction for future research. Growth hormone pituitary tumours are characterised by the secretion of growth hormone, which stimulates the production of insulin-like growth factor-1, and our study found that insulin-like growth factor 1 promotes pituitary tumour development, creating a vicious cycle. Insulin-like growth factor-1 may provide a new approach for the pharmacological treatment of growth hormone-induced pituitary tumours. In previous clinical studies, the growth hormone/insulin-like growth factor-1 axis was found to increase the growth rate of meningiomas [72], which is inconsistent with our finding that insulin-like growth factor 1 is negatively regulated in benign meningiomas, highlighting the need for further research into the various components of the growth hormone/insulin-like growth factor-1 axis in the pathogenesis of meningiomas.

The sample size of this statistical analysis was sufficiently large, and we considered it to have high validity. We performed a co-localisation analysis of the positive results, which further enhanced the confidence of our findings. Our application of MR worked well to avoid confounding factors and determine the relationship between exposure factors and outcomes. However, our study has some limitations. First, the population we chose to study was predominantly European; therefore, the conclusions we drew may lack generalisability. Second, we failed to stratify the data on exposures and outcomes, and our results were insufficiently explored. Due to data limitations, we were also unable to obtain validated prognostic markers to enrich our study. Observational experiments suggest a sex-based difference in patients with meningiomas, whereas we obtained the data as a whole and were unable to obtain more suggestive results. We were also unable to stratify the meningiomas to obtain an association between different grades of meningioma and exposure. We were also unable to classify patients with pituitary tumours in further studies. Unfortunately, we are also unable to classify spinal cord tumours for study. Finally, we were unable to elucidate the biological mechanisms involved in multiple dimensions, such as multi-omics, gene, environment, and the duration of action.

Conclusion

We identified T2DM as a risk factor for glioblastoma, insulin-like growth factor1 as a protective factor for benign meningiomas and as a risk factor for pituitary tumours and craniopharyngiomas, and fasting glucose and glycated haemoglobin as risk factors for benign cord tumours. The above conclusions are mainly based on the IVW method. Additionally, we did not find phenotypes that shared causal variants in the co-localisation analysis. Our findings provide a new direction for exploring the relationship between glucose and related factors in CNS tumours, which requires further investigation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-024-03969-6.

Supplementary Material 1

Author contributions

Yongxue Li designed the study. Lihao Lin analysed the datasets and interpreted the results. Wenhui Zhang downloaded the data. Yan Wang wrote and edited the manuscript. Yi Guan provided the foundation and support for this study. All the authors have read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available from the GWAS repository at https://gwas.mrcieu.ac.uk and from the Finngen database at https://www.finngen.fi; however, restrictions apply to the availability of these data, which were used under licence for the current study and are not publicly available. The data are available from the authors upon reasonable request and with permission from the GWAS repository and Finngen database.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publish

Not applicable.

Competing interests

The authors declare no competing interests.

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