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Original article

Does diabetes decrease the risk of glioma? A systematic review and meta-analysis of observational studies

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ABSTRACT

Purpose: Increasing epidemiologic evidence suggests that diabetes mellitus (DM) may be associated with a decreased risk of glioma. This systematic review assessed whether DM was associated with glioma risk.
Methods: Electronic searches were performed in PubMed, Web of Science, EMBASE, and Cochrane Library databases up to August 30, 2018. A random-effects model was performed to calculate summary effect size with corresponding 95% confidence intervals (CIs).
Results: In total, 10 studies (eight case–control studies and two cohort studies) matched the inclusion criteria. Meta-analyses of case–control studies showed that DM decreased the risk of glioma by 23% (odds ratio: 0.77, 95% CI: 0.61–0.96; $P = .02$, $I^2 = 82.0\%$). However, no such effect was observed in cohort studies (relative risk: 0.71, 95% CI: 0.10–4.80; $P = .72$, $I^2 = 61.6\%$). In the subgroup analyses, DM was associated with a decreased risk of glioma in Caucasians but not in Asians; the inverse association was slightly higher in males than in females.
Conclusions: Our results indicate that DM decreases the risk of glioma, but the inverse association may vary in subgroups. The present conclusions should be confirmed with further studies.

Introduction

Glioma is the most common primary central nervous system tumor in adults, accounting for 70%–80% of all malignant brain tumors [1,2]. Glioma is usually subdivided into four grades including grades I, II, III, and IV according to their degree of malignancy [3]. Glioblastoma (GBM), the most common and aggressive type of malignant primary tumor, has a median survival time of 14.6 months and less than 5% of GBM patients survive 5 years with standard therapy [4]. The potential risk factors for glioma include allergic/atopic diseases, genetic factors, and ionizing radiation exposures [5,6], but the etiology of glioma remains largely unknown.

Diabetes mellitus (DM) is one of the major public health issues in both developed and developing countries. Epidemiologic evidence suggests that DM is associated with increased risk of several cancers including the pancreas, liver, endometrium, colorectum, kidney, breast, and bladder [7–16]. Interestingly, in 2016, one meta-analysis combining 11 studies suggested that the risk of glioma among diabetic patients was 21% lower than that among individuals without DM [17]. However, this study did not clearly distinguish glioma and brain cancer, resulting in some of the subjects included were brain cancer patients [18–21]. In addition, there were few subgroup analyses. To date, many new epidemiologic studies have been conducted to explore the relationship between DM and glioma risk, but these findings were somewhat contradictory and inconclusive, especially when stratifying for types of DM and glioma [22,23]. Several studies obtained null associations between type II DM (T2DM) and glioma risk [22,24,25]. Barami et al. [24] found that DM might increase the incidence of GBM by up to 100% in White populations compared with Black people.

Considering that long-term randomized clinical trials are impossible to implement on a practical basis, case–control and cohort studies are considered as the best evidence available to

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assess the association between DM and risk of glioma. Therefore, we included all recently published case–control and cohort studies in this meta-analysis.

Methods

Search strategy

We conducted this meta-analysis by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [26]. Two independent investigators (W.Y.B. and L.X.X.) searched in PubMed, Web of Science, EMBASE, and Cochrane Library databases from their inception to August 30, 2018. According to the traditional classification of glioma by histologic type and malignancy [27], the initial search was elaborated on PubMed using the strategy: (astrocytoma OR oligodendroglioma OR glioblastoma OR medulloblastoma OR glioma OR brain cancer OR Glioma [MeSH Terms]) AND (diabetes mellitus [MeSH Terms] OR diabetes OR DM) AND (incidence OR risk OR risk [MeSH Terms]). We selected case–control and cohort studies that had been published in English. To find any additional published studies, a manual search was also performed by checking all the references of all the studies. The reviewers (W.Y.B. and L.X.X.) determined the eligibility of studies by reading the title, abstract, or full text.

Selection criteria

Studies were required to meet the following inclusion criteria to be eligible for inclusion in the meta-analysis: (1) case–control studies that recruited glioma cases and controls without glioma; (2) cohort studies conducted among diabetic patients and healthy individuals to estimate the glioma risk; (3) the exposure of interest was the presence of pre-existing DM, and the main outcome of interest was the incidence of glioma; (4) the sample size with glioma be available; (5) effect sizes (ES) (including odds ratio [OR], relative risk [RR], or hazard ratio) and the corresponding 95% confidence intervals (95% CIs) were reported, and only studies with adjusted risk estimates should be included. If there were multiple publications from the same study, the most complete or most recent publication was given precedence. A fixed effects model was used to calculate the risk for all patients combined in a study when risk estimates were only given for males and females separately, and this combined ES was used for further meta-analysis [28].

Reviews, editorials, commentaries, and conference abstracts were excluded from our analysis.

Data extraction

Data extraction was conducted independently by two investigators (W.Y.B. and L.X.X.), with disagreements resolved by consensus. The following data were abstracted from each article in a standard format: the first author, publication year, source of control group (population based or hospital based), study location, study region, study period and duration of follow-up, participant's age range, the number of glioma and DM patients, and criteria used to evaluate glioma and DM. We also collected data on the analytical approach, adjusted effect estimates and its 95% CIs, and confounding factors.

Quality assessment

The quality of the study was assessed using the nine-star Newcastle–Ottawa Scale (NOS; range: 0 to 9) [29]. Three aspects were considered in the NOS criteria: (1) subject selection (0–4 stars); (2) comparability of subject (0–2 stars); and (3) assessment of outcome (0–3 stars). A study with ≥7 awarded stars was defined as a high-quality study, and 0–6 stars as low quality.

Statistical analysis

We used a random effects model to calculate summary ES and 95% CI for the association between DM and glioma risk. Degree of heterogeneity was interpreted using the I^2 statistic [30]: low (I^2: <33%), moderate (I^2: 33.1%–66%), or high (I^2: 66.1%–100%). For the Q statistic, a P value less than .10 was considered statistically significant [31]. For subgroup analysis, the characteristics of the studies were combined accordingly: study designs (cohort and case–control), control selection (hospital and population), gender (males and females), race(Caucasians and Asians), analytical approach (Logistic regression, Poisson regression, Mendelian randomization, and Mantel–Haenszel), quality of the study (7 or more and less than 7), type of DM (only T2DM, type I diabetes [T1DM] and T2DM, and type not reported), sample size (the number of glioma patients <500 and ≥500), criteria for DM diagnosis (Read codes, fasting plasma glucose, questions inquiring of physician diagnosis, self-reported history, and not applicable), criteria for glioma diagnosis (Read codes or not applicable), the pathology grade of glioma (high-grade glioma [World Health Organization (WHO) grades III and IV], low grade glioma [WHO grades I and II]), and the classification of morphology of glioma. One at a time, each study characteristic was entered as covariate in the meta-regression model. We assessed the influence of individual studies on the summary effect estimate by omitting one study at a time when recalculating the summary ES. Potential publication bias was assessed by visual inspection of the funnel plot. Moreover, the Begg's rank correlation and Egger's linear regression tests were performed (significance level at $P < .10$) [32]. All analyses were performed using Stata, version 14.0 (StataCorp, College Station, TX). A P value <.05 was considered statistically significant.

Results

Literature search

Of the 2879 articles originally identified, we excluded 514 duplicates (i.e., those that appeared in more than one database or from more than one set of search terms). Another 2343 articles were excluded after screening the title and abstract. For the remaining 28 articles, we conducted a full-text assessment for relevance. Eighteen articles were excluded for the reasons listed in Figure 1. Finally, 10 studies [22–25,33–38] met the criteria for entering the meta-analysis.

Description of included studies

The main details of the included studies were listed in Table 1. These 10 studies, consisted of eight case–control studies [22–25,33–36] and two cohort studies [37,38], were published between 1989 and 2018. The sources of controls were composed of two parts. One was from a country [23–25,33,34,36–38], and the other one was from multiple countries or regions [22,35]. We also observed that eight studies were population-based studies [22–24,33,35–38], and two studies were hospital-based studies [25,34].

Appendix Table 2 displays the quality assessment of each study according to the NOS criteria. After assessment of risk bias, three case–control studies [22,24,36] were assigned six stars. The remaining seven studies [23,25,33–35,37,38] received from 7 to 8 stars (Appendix Table 1).

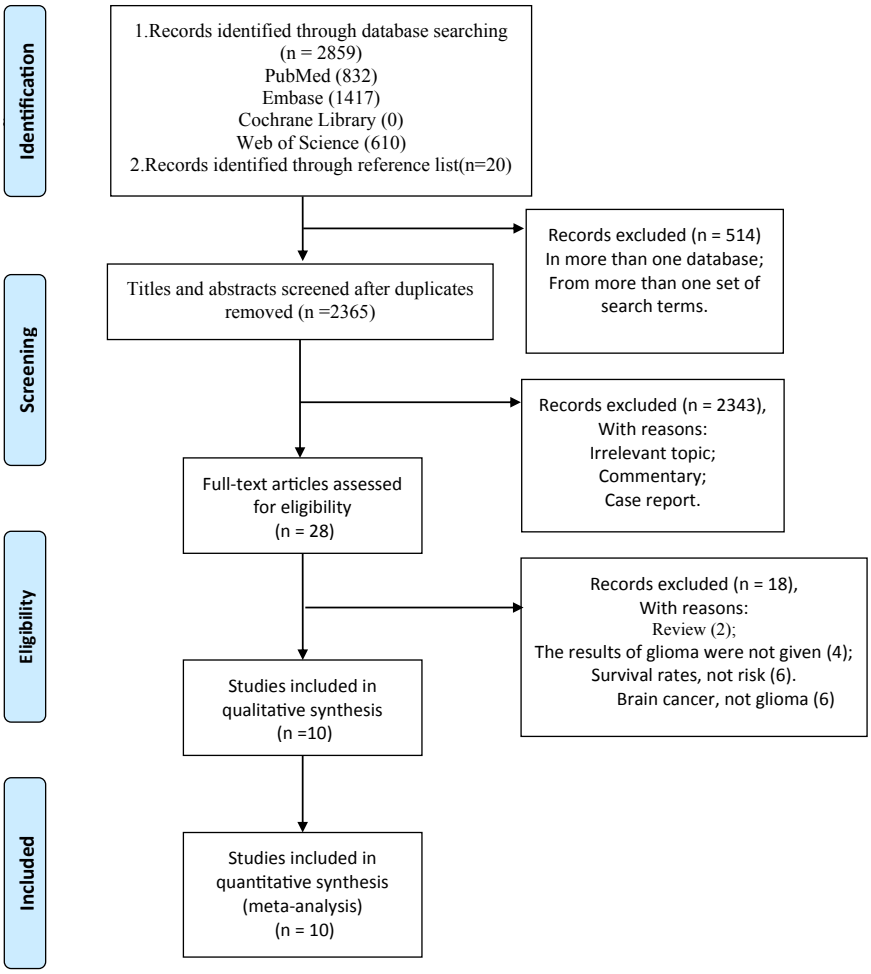

Fig. 1. PRISMA flow diagram for identification of relevant articles for the meta-analysis.

Quantitative synthesis

Overall analysis

As shown in Table 2 and Figure 2, patients with DM were at a reduced risk for glioma compared with nondiabetic people in case–control studies (OR = 0.77, 95% CI: 0.61–0.96; I^2 = 82.0%). Although no such effect was observed in cohort studies (RR = 0.71, 95% CI: 0.10–4.80; I^2 = 61.6%). The association of diabetes and glioma risk was not dependent on any single study (Appendix Fig. 1). Meanwhile, the negative association was not essentially altered on exclusion of three studies [22,24,36] receiving less than seven stars after quality assessment (ES = 0.68, 95% CI: 0.57–0.82; $P < .001$).

Meta-regression analysis

In the univariate meta-regression model, the number of glioma patients, type of diabetes, and quality of study had statistical significance (Table 2).

Subgroup analysis

Analyses stratified by control selection showed that DM was associated with a reduced risk of glioma for population-based studies. When the risk estimates were stratified by gender, a significant inverse association was found among males [23,33], and the negative association was slightly lower among females [23,33]. In addition, in the subgroup analysis of races, five studies [23,35–38] were carried out among Caucasians. The summary ES was 0.67 (95% CI: 0.50–0.89; $P = .005$). Only one study carried out among Asians [25], and the result showed no significance. Notably, there was a significant negative association between DM and glioma risk when the number of glioma patients was less than 500 [33,34,36–38]. However, the association was not apparent with a larger sample size (500 or more) [22–25,35]. Subsequently, the analysis stratified by analytical approach found a significant association between DM and glioma risk by logistic regression [23–25,33–36]. In addition, the association was found for those studies including both T1DM and T2DM [33,36,37] or the types of DM were not reported [23,34,35,38]. On the contrary, the association was not found for three studies that included T2DM only [22,24,25]. Two studies [22,23] used Read codes, and one study [25] used fasting plasma glucose as criteria for DM diagnosis showed no association between DM and glioma risk. Moreover, two studies [34,38] used self-reported or questions inquiring of physician-diagnosed also showed no significant association. But seven studies [23,24,33,35–38] used Read codes from medical records as criteria for glioma diagnosis showed a significant inverse association between DM and risk of glioma (Table 2).

In total, three studies [22,23,33] took the pathologic grade of glioma into account. Relative to risk of glioma among nondiabetic patients, a diagnosis of DM was not associated with the risk of high-grade glioma (WHO grades III and IV). For low-grade glioma (WHO grades I and II) [23], the association was also no significance. In addition, two studies took the classification of morphology of

Table 1
Main characteristics of the studies included in the meta-analyses

First author, y (reference no.)	Study design	Source of controls	Country/ region	Race	Sample	Study period	Glioma type	Type of diabetes	Criteria for diabetes diagnosis	Criteria for glioma diagnosis	Analytical approach	No. of glioma	No. of diabetes	Effect size and 95% CI	Control for confounding	NOS scores
Schleofer (1999) [35]	Case–control	International population-based	France, Australia, Canada, Germany, Sweden, the United States	Caucasian	Age = 20–75 y, male = 54%	1980–1991	The major histologic subtypes among gliomas were astrocytic tumors	NA	NA	ICD-O code 191	Conditional logistic regression	1178	107	All: 0.82 (0.52–1.28)	Matching frequency, sex, age, post code, urban/ rural, ethnicity, parish	7
Cicuttini (1997) [36]	Case–control	Population-based	Australia	Caucasian	Age = 48.9 y, male = 60.1%	1987–1991	Primary glioma	Mixed	NA	ICD-O codes 938–946	Logistic regression	416	14	All: 0.34 (0.11–1.05)	Adjustment for age, sex	6
Mills (1989) [38]	Cohort	Population-based	The United States	Non-Hispanic White	Age = 25 y or older, male = 57%	1976–1982	GBM, astrocytoma	NA	Life-style questionnaire	Medical record	Mantel–Haenszel	21	6 y of follow-up, 9499 person-years	All: 1.84 (0.28–7.38)	Age- and sex-adjusted	8
Brenner (2002) [34]	Case–control	Hospital patients	The United Studies	Non-Hispanic White; Hispanic White; Black	Age = 18–90 y, male = 57%	1994–1998	Histologically confirmed intracranial glioma	NA	Self-reported information and questions inquiring of physician-diagnosed	NA	Conditional and unconditional multivariate logistic regression	473	785	All: 0.44 (0.27–0.70)	Adjustment for age, sex, race or ethnicity, and distance of residence from hospital	8
Schwartzbaum (2005) [33]	Case–control	Swedish Population Registry	Sweden	Caucasian	Age = 32–77 y, male = 56%	1987–1999	Low-grade glioma; HGG; a sufficient number of GBM and anaplastic astrocytoma	Mixed	NA	Read codes	Unconditional logistic regression	Low-grade glioma: 38; HGG:183; GBM:45	5224	All: 0.64 (0.52–0.80) HGG, males: 0.65 (0.49–0.86), females: 0.63 (0.44–0.90)	Adjustment for age, sex, and year of diagnosis or reference year	7
Swerdlow (2005) [37]	Cohort	Population-based	The United Kingdom	Caucasian	Age = 30–49 y, male = 58.1%, follow-up = 18.0 y	1972–1993	NA	64% type II and 36% type I	NA	Read codes	Poisson regression	2	5066	All: 0.26 (0.03–0.94)	Adjustment for age, sex, calendar-year, and country-specific person-years	7
Gong (2012) [25]	Case–control	Hospital-based: healthy cohorts or patients with other cancers	China	The majority was Han people	Age = 30–79 y, male = 60%	2004–2008	NA	Type II	FPG > 7.8 mmol/ L at least twice	NA	Multivariable unconditional logistic regression	674	NA	All: 1.06 (0.65–1.72)	Adjustment for HBsAg, sex, age, and family history of cancer	8
Seliger (2015) [23]	Matched case–control	Without a glioma history from the CPRD	The United Kingdom	UK population	Age = 55.5 (±18.7) y, male = 55.2%	1995–2012	Grade IV only, grade III or IV, and grade II	NA	Specific Read codes	Read codes for glioma	Conditional logistic regression	2005	1336	All:0.74 (0.60–0.93); men: 0.70 (0.53–0.92), women: 0.84 (0.59–1.19); GBM: 0.69 (0.51–0.94); Grade III or IV glioma: 0.74 (0.55–0.99); Grade II glioma:1.12 (0.49–2.56)	Matched on age, sex, general practice, number of years of active history in the database, adjusted for	8

(*continued on next page*)

Table 1 (*continued*)

First author, y (reference no.)	Study design	Source of controls	Country/ region	Race	Sample	Study period	Glioma type	Type of diabetes	Criteria for diabetes diagnosis	Criteria for glioma diagnosis	Analytical approach	No. of glioma	No. of diabetes	Effect size and 95% CI	Control for confounding	NOS scores
															BMI and smoking	
Barami (2017) [24]	Retrospective case–control	Randomly selected from the KPNC population	The United States	White; Non-White	Age = 65 y, male = 55.4%	2000–2013	GBM multiforme	Type II	NA	New GBM diagnoses based on WHO diagnostic criteria	Conditional logistic regression	969	168	All: 0.90 (0.70–1.20)	Adjustment for sex, age, year of GBM diagnosis	6
Disney-Hogg (2018) [22]	Case–control	Genome-wide association study data	Europe	European descent	NA	NA	Pilocytic astrocytoma WHO grade I, diffuse "low-grade" glioma WHO grade II, anaplastic glioma WHO grade III, and GBM WHO grade IV	Type II	SNPs for type II diabetes were identified	NA	Generalized summary data-based mendelian randomization	12,488	NA	All: 1.04 (0.97–1.11); GBM multiforme: 1.00 (0.92–1.08); Non-GBM multiforme: 1.08 (0.99–1.18)	Adjustment for age, gender, and ethnicity	6

FPG = fasting plasma glucose; HBsAg = Hepatitis B surface antigen; HGG = high-grade glioma; ICD = International Classification of Disease; NA = not available; SNPs = single-nucleotide polymorphisms.

glioma into account [22,23]. The association between GBM risk associated with DM was not apparent (Table 2).

Publication bias

The funnel plot (Appendix Fig. 2) showed some asymmetry reflecting the relative absence of studies with small sample sizes and inverse associations in overall analysis. Results from the Begg's test revealed that there was no obvious publication bias among the case–control studies ($P = 1.00$). However, Egger's test showed an obvious publication bias in the case–control studies ($P = .035$).

Discussion

Our meta-analysis indicates that DM was associated with a statistically significant decrease in glioma risk of 23% in case–control studies. However, there was no association between DM and glioma risk among cohort studies. Through subgroup analyses, this negative association was observed clearly in the population-based studies, in Caucasians, and both in males and females. When we carried out the "leave one out" sensitivity analysis as the criterion, our meta-analysis showed no significance between study heterogeneity. After exclusion of three articles [22,24,36] that were less than seven stars after quality assessment, the negative association was not essentially altered. The estimate should be cautiously interpreted despite the significant association obtained in this study because of the heterogeneity and inconsistency of the studies included and the lack of association among cohort studies.

Our results demonstrated that some methodological aspects have direct influence on this association. We included several newly published case–control and cohort studies in this meta-analysis, which allowed a more detailed and accurate risk estimate than that of a prior meta-analysis [17]. The results of the meta-regression and subgroup analyses revealed that the sample size explained approximately 63.91% of the variability between studies (Table 2). As confirmed by previous studies, small sample size may overestimate the association between presumed exposure and outcome [39]. Indeed, among the studies included in our meta-analysis, we could observe that most of the small studies did not present a representative sample (e.g., type of DM, criteria for DM diagnosis was not available). Large population-based studies with representative samples are scant. Moreover, different statistical methods, such as logistic regression model or Poisson regression, may also result in deviations.

T1DM and T2DM have distinct pathophysiology and therefore affect tumor biology differently. T1DM is known to have an early onset and autoimmune component, and the age-dependency of glioma risk might imply that T1DM is more negatively associated with glioma. It is worth noting that the association was not significant when the subjects were T2DM only. Barami et al. [24] found that there was no association between T2DM and risk of GBM. Similarly, Disney-Hogg et al. [22] found no evidence to support a relationship between T2DM with subtypes of GBM or non-GBM tumors. Moreover, Gong et al. [25] showed that there was no association between T2DM and GBM risk for Han people age ranged 30–79 years by fasting plasma glucose as the criteria for DM diagnosis.

The association between the DM and the histologic type and malignancy of glioma risk has been assessed in a few studies, but inconsistent results were obtained. Seliger et al. [23] observed that glioma risk was more pronounced in grade III or IV than grade I or II. Schwartzbaum et al. [33] found a more statistically significant association between DM and risk of high-grade gliomas, regardless of gender. However, In the study of Disney-Hogg et al. [22], no evidence to support the relationship between T2DM with subtypes of GBM or non-GBM tumors. The subgroup analyses were based on only a few studies, and we recommend further studies of high quality be conducted in this field.

Table 2
The results of subgroup analyses and meta-regression analyses

Subgroup	Number of studies	Heterogeneity			Subgroup analysis		Meta-regression
		Q value	*P* value	I^2 (%)	ES (95% CI)	*P* value	*P* value
Type of design of studies							.936
Case–control study	8	38.80	<.001	82.0	0.77 (0.61–0.96)	.021	
Cohort study	2	2.61	.106	61.6	0.71 (0.10–4.80)	.721	
Control selection							.620
Hospital control	2	6.41	.011	84.4	0.68 (0.29–1.61)	.384	
Population control	8	31.20	<.001	77.6	0.79 (0.63–0.99)	.049	
Gender							.680
Male	2	0.14	.712	0.0	0.68 (0.55–0.82)	<.001	
Female	2	1.27	.260	21.0	0.73 (0.55–0.97)	.028	
Race							.183
Caucasians	5	4.93	.294	18.9	0.67 (0.50–0.89)	.005	
Asians	1	0.00	—	—	1.06 (0.65–1.72)	.814	
Type of diabetes							.006
Only type II	3	1.05	.591	0.0	1.03 (0.97–1.10)	.345	
Type I and type II	3	2.15	.341	7.0	0.59 (0.43–0.82)	.001	
Type not reported	4	5.70	.127	47.4	0.69 (0.50–0.95)	.023	
Analytical approach							.295
Logistic regression	7	12.38	.054	51.5	0.72 (0.60–0.88)	.001	
Poisson regression	1	0.00	—	—	0.26 (0.05–1.50)	.125	
Mendelian randomization	1	0.00	—	—	1.04 (0.97–1.11)	.254	
Mantel–Haenszel	1	0.00	—	—	1.84 (0.36–9.45)	.465	
Number of glioma							.020
<500	5	5.64	.227	29.1	0.55 (0.39–0.77)	.001	
500 and beyond	5	9.94	.041	59.8	0.91 (0.77–1.08)	.286	
Diabetes diagnosis							.446
Read codes	2	8.46	.004	88.2	0.90 (0.64–1.24)	.500	
FPG	1	0.0	—	—	1.06 (0.65–1.72)	.814	
Self-reported/questions inquiring	2	2.71	.100	63.1	0.72 (0.19–2.73)	.629	
NA	5	7.14	.129	44.0	0.72 (0.56–0.93)	.012	
Glioma diagnosis							.584
Read codes	7	8.39	.211	28.5	0.74 (0.62–0.88)	.001	
NA	3	12.30	.002	83.7	0.81 (0.49–1.34)	.407	
Pathologic grades of glioma							.562
High grade (WHO grade III or IV)	3	17.03	<.001	88.3	0.79 (0.58–1.09)	.149	
Low grade (WHO grade I or II)	1	0.0	—	—	1.12 (0.49–2.56)	.788	
Morphology of glioma							—
GBM	2	5.29	.021	81.1	0.86 (0.60–1.23)	.397	
Quality							.084
≥7	7	10.44	.107	42.5	0.68 (0.57–0.82)	.001	
<7	3	4.74	.093	57.8	0.94 (0.73–1.20)	.618	

FPG = fasting plasma glucose; NA = not available.

Possible underlying biologic mechanisms of the negative association between DM and glioma risk are poorly known. The inverse association may reflect a protective effect of heightened immune response [40]. Kasper et al. found that advanced stages of DM are associated with higher levels of insulin-like growth factor (IGF)-binding protein 3, lower levels of circulating insulin, and IGF-1 [41]. Trojan et al. observed that IGFs show enhanced expression in glioma [42]. Moreover, IGF-1 has mitogenic potential in glioma cells [42]. Thus, the decrease in signal through IGFs and insulin represents a potential pathway to explain the inverse association between DM and glioma risk.

Our study has several strengths as follows: (1) we were able to include a number of more recently published studies on the DM–glioma association; (2) we could derive risk estimates with high levels of precision because we conducted our analysis according to more than 20,000 glioma cases; (3) this is the first meta-analysis focusing on the association between different types of DM and glioma.

Our study has several limitations. First, lack of cohort studies is a major limitation. Case–control studies are subject to recall bias and selection bias. Future cohort studies are especially warranted.

Second, there are few biologic evidence on the association between DM and incident cases of glioma, and glioma status in most of the studies was based on Read codes from medical records, which may lead to some misclassification.

Third, because glucose levels might have been used as a covariate for analysis adjustment in studies not captured with our search strategy, it is not possible to guarantee that all data in the literature regarding the association between DM and glioma risk were included in this meta-analysis. Nevertheless, it is expected that the comprehensive search in four broad databases identified most of the observable studies available.

Fourth, although 10 studies in this study have adjusted for some potential confounders, only one of them included at least age, sex, general practice, smoking, and a weight-related variable in the analysis [23]. Therefore, we were unable to observe the results of control for physical activity or other lifestyle factors. But prior studies have suggested there were no meaningful associations between lifestyle factors (smoking status, alcohol intake, socioeconomic level, parity, age at first birth, and oral contraceptive use) and glioma risk [43]. However, a meta-analysis [44] found that high versus low physical activity levels showed a weak inverse association with glioma risk.

Fifth, most of the studies did not distinguish T1DM from T2DM. However, the mixture of these two conditions is not likely to have significantly affected our results because T2DM generally accounts for majority of prevalent diabetes in older individuals. However, when we restricted the meta-analysis to those studies that consisted of T2DM only, the relationship between DM and glioma risk

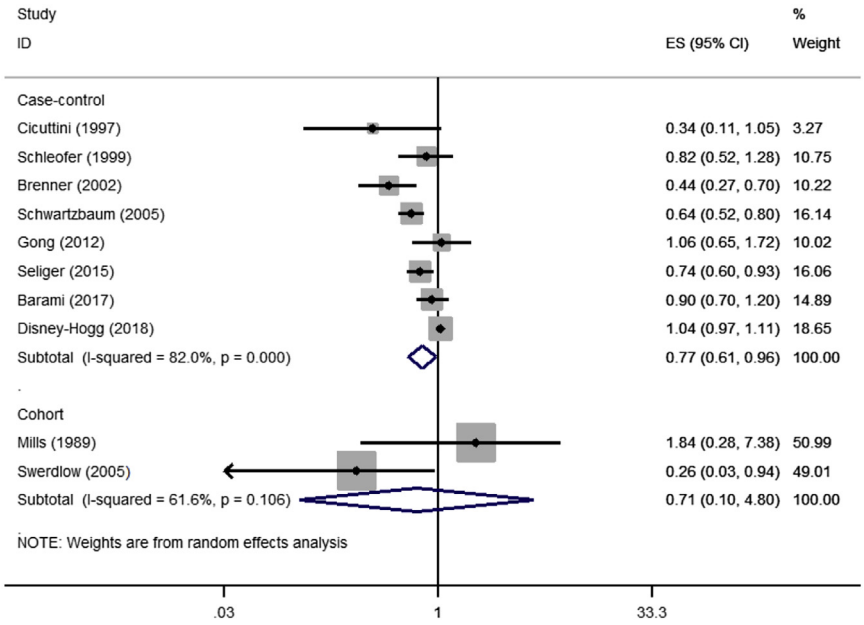

Fig. 2. Summary effect size of diabetes mellitus on glioma risk. Data are presented as effect size (ES) for each study (boxes), 95% CIs (horizontal lines), and summary as ES with 95% CI (diamond).

was significantly altered. But the subgroup analyses of T2DM were based on only three studies, and the results need to be interpreted with caution.

Sixth, so far, one matched case–control study has reported that antidiabetic treatment did not influence the glioma risk, but a potential protective effect of metformin use on glioma risk cannot be entirely excluded [23,45–48]. However, DM duration and treatment were not available in most included studies and thus could not be taken into the analyses.

Seventh, an inverse relationship between increased HbA1C and risk of glioma has been reported in some studies [49–51]. However, the data were not available in our study.

Finally, the funnel plot showed some asymmetry and Egger's test showed an obvious publication bias in case–control studies, and the presence of publication bias may result in an overestimate of the relationship between DM and glioma risk.

Conclusions

Our results indicate that DM decreases the risk of glioma, but the inverse association may vary in subgroup analyses. Our finding should be confirmed with additional studies that address the potentially confounding factors.

Acknowledgments

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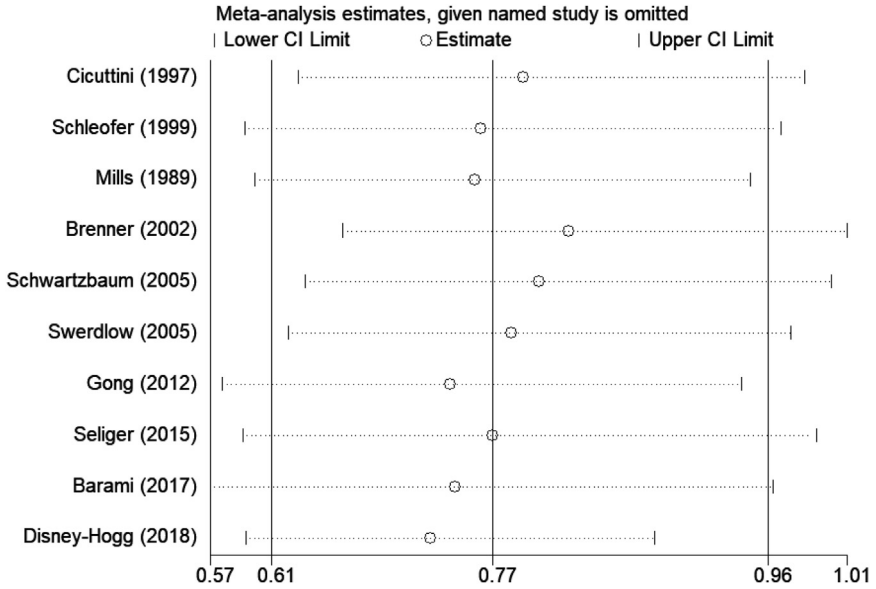
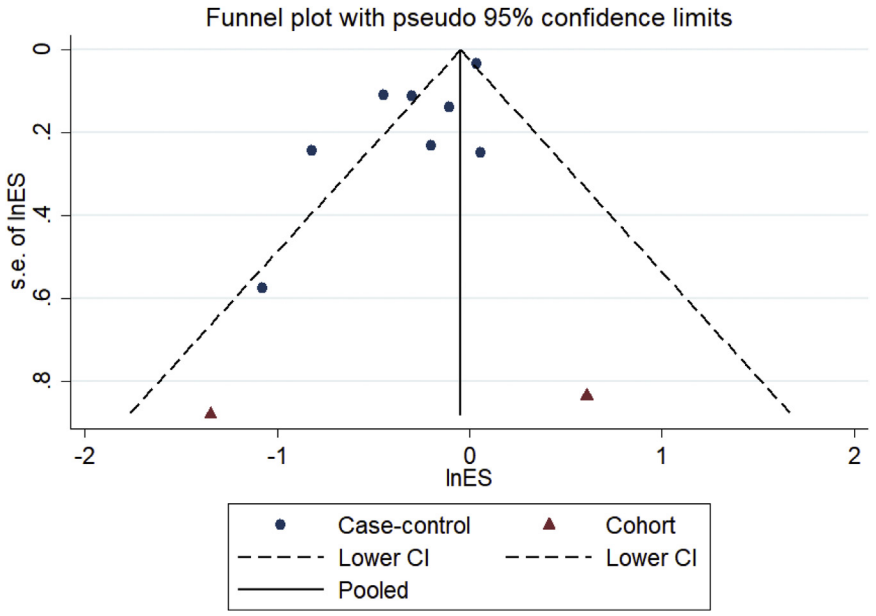
Appendix



Appendix Fig. 1. Sensitivity analysis demonstrating the influence of each study in the summary effect of diabetes mellitus on the risk of glioma. Data are presented as new overall relative risk for each study omission (circles) and 95% CI (horizontal lines).



Appendix Fig. 2. Funnel plot analysis of the publication bias of the articles included about diabetes mellitus and risk of glioma. ES, effect size.

Appendix Table 1
Search strategies for electronic databases

Engine	Strategy	
Cochrane Library	#1	MeSH descriptor Glioma explode all trees
	#2	glioma
	#3	astrocytoma
	#4	oligodendroglioma
	#5	glioblastoma
	#6	medulloblastoma
	#7	brain tumor
	#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
	#9	MeSH descriptor diabetes mellitus explode all trees
	#10	diabetes
	#11	DM
	#12	(#9 OR #10 OR #11)
	#13	risk
	#14	incidence
	#15	(#13 OR #14)
	#16	(#8 and #12 and #15)
EMBASE	#1	'Glioma'/exp
	#2	glioma
	#3	astrocytoma
	#4	oligodendroglioma
	#5	glioblastoma
	#6	medulloblastoma
	#7	brain tumor
	#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
	#9	'diabetes mellitus'/exp
	#10	Diabetes
	#11	DM
	#12	#9 OR #10 OR #11
	#13	'risk'/exp
	#14	Risk
	#15	incidence
	#16	#13 OR #14 OR #15
	#17	#8 and #12 and #16
Web of Science	#1	TS = (glioma)
	#2	TS = (astrocytoma)
	#3	TS = (oligodendroglioma)
	#4	TS = (glioblastoma)
	#5	TS = (medulloblastoma)
	#6	TS = (brain tumor)
	#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
	#8	TS = (diabetes mellitus)
	#9	TS = (diabetes)
	#10	TS = (DM)
	#11	#8 OR #9 OR #10
	#12	TS = (risk)
	#13	TS = (incidence)
	#14	#12 OR #13
	#15	#7 and #11 and #14
PubMed	#1	"Glioma" [Mesh]
	#2	glioma
	#3	astrocytoma
	#4	oligodendroglioma
	#5	glioblastoma
	#6	medulloblastoma
	#7	brain tumor
	#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
	#9	"diabetes mellitus" [Mesh]
	#10	diabetes
	#11	DM
	#12	#9 OR #10 OR #11
	#13	"risk" [Mesh]
	#14	risk
	#15	incidence
	#16	#13 OR #14 OR #15
	#17	#8 AND #12 AND #16

Appendix Table 2
Methodological quality assessment of the included studies

First author	Year	Selection				Comparability	Outcome			Total
Cohort		Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Presentation of outcome as start	Control for important factor	Assessment of outcome	Sufficient follow-up time	Appropriate follow-up	Score (0–9)
Swerdlow [37]	2005	1	1	0	1	2	1	1	0	7
Mills [38]	1989	1	1	1	1	1	1	1	1	8
Case–control		Selection	Comparability	Outcome	Total					
		Adequate definition of cases	Representativeness of cases	Selection of control	Definition of control	Control for important factor	Ascertainment of exposure (blinding)	Same method of ascertainment	Nonresponse rate	Score (0–9)
Schleofer [35]	1999	1	0	1	1	2	1	1	0	7
Cicuttini [36]	1997	1	0	1	1	1	1	1	0	6
Brenner [34]	2002	1	1	1	1	2	1	1	0	8
Schwartzbaum [33]	2005	1	0	1	1	2	1	1	0	7
Gong [25]	2012	1	1	1	1	2	1	1	0	8
Seliger [23]	2015	1	1	1	1	2	1	1	0	8
Barami [24]	2017	1	1	1	1	1	1	0	0	6