

## The worldwide incidence and prevalence of primary brain tumors: a systematic review and meta-analysis

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**Background.** Primary brain tumors are a heterogeneous group of benign and malignant tumors arising from the brain parenchyma and its surrounding structures. The epidemiology of these tumors is poorly understood. The aim of our study is to systematically review the latest literature on the incidence and prevalence of primary brain tumors.

**Methods.** The systematic review and meta-analysis were conducted according to a predetermined protocol and established guidelines. Only studies reporting on data from 1985 onward were included. Articles were included if they met the following criteria: (i) original research, (ii) population based, (iii) reported an incidence or prevalence estimate of primary brain tumors.

**Results.** From the 53 eligible studies overall, 38 were included in the meta-analysis. A random-effects model found the overall incidence rate of all brain tumors to be 10.82 (95% CI: 8.63–13.56) per 100 000 person-years. The incidence proportion estimates were heterogeneous, even among the same tumor subtypes, and ranged from 0.051 per 100 000 (germ cell tumors) to 25.48 per 100 000 (all brain tumors). There were insufficient data to conduct a meta-analysis of the prevalence of primary brain tumors.

**Conclusions.** There is a need for more accurate and comparable incidence and prevalence estimates of primary brain tumors across the world. A standardized approach to the study of the epidemiology of these tumors is needed to better understand the burden of brain tumors and the possible geographical variations in their incidence.

**Keywords:** brain tumor, incidence, meta-analysis, prevalence, systematic review.

Primary brain tumors are a heterogeneous group of benign and malignant tumors arising from the brain parenchyma and its surrounding structures. These tumors are an important cause of morbidity and mortality in both adults and children, often generating severe disabilities and producing high burden in both families and health care systems.<sup>1,2</sup> The epidemiology of these tumors is poorly understood, as there is a paucity of data published on their incidence and prevalence across the globe. A solid understanding of the incidence and prevalence of primary brain tumors can help with better planning in the allocation of health resources and a better understanding of geographical differences.

Only one systematic review on the worldwide incidence of brain tumors has been published within the last 20 years.<sup>3</sup> The paper, published in 1998, reviewed the methodology and

results of studies including not only primary, but also secondary intracranial tumors. The world age-standardized incidence rate for all primary brain tumors reported in this review ranged from 4.3 to 18.6 per 100 000 per year. Unfortunately, this review had methodological limitations. The authors searched only English-language papers published from 1966 to 1995 (including data collected from 1935 to 1991) and included studies that were not population based in the review, which could result in biased estimates. Only one bibliographical database (Medline) was used for the search, and a formal meta-analysis of incidence rates was not performed. There was also marked heterogeneity in the methodology and results of the different studies included in the review.

There is a lack of a comprehensive and up-to-date systematic review of the global incidence and prevalence of brain

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tumors in the literature. The goal of our study was to systematically review the latest literature on incidence and prevalence of primary brain tumors.

## Methods

### Search Strategy

The systematic review and meta-analysis were conducted according to a predetermined protocol and established guidelines (Meta-analysis Of Observational Studies in Epidemiology, MOOSE).<sup>4</sup> The search strategy (Supplementary Appendix A) was developed by the study authors with expertise in brain tumors and epidemiology and in consultation with a research librarian with systematic review expertise. The search was conducted on December 10, 2010 in Medline and on December 12, 2010 in Embase databases, and references were exported and managed using EndNote X5. Only studies reporting on data from 1985 onward were included, as prior to this date MRI, which has revolutionized the diagnosis of many neurological disorders, was not in clinical use. If a paper reported on data prior to and after 1985, only data exclusively from 1985 or later were included. Articles were included if published in English or French. Review articles on the epidemiology of brain tumors and the reference lists of articles that met inclusion criteria were also hand-searched for additional articles.

### Study Selection

Abstracts and titles of all references were screened independently and in duplicate, to identify original research that reported on the prevalence or incidence of all primary brain tumors (malignant or nonmalignant). Those that were clearly not population based were excluded at this stage. Subsequently, 2 reviewers independently screened the full-text articles of abstracts identified in the first phase. Articles were included if they met all of the following criteria: (i) original research, (ii) population based, (iii) reported an incidence or prevalence estimate of primary brain tumors. Disagreements pertaining to the inclusion of articles were resolved by consensus and involvement of a third party as necessary.

### Data Extraction

Two reviewers extracted and reached agreement on data from included articles using a standard data collection form. When multiple articles reporting data from the same study population were encountered, the most comprehensive data were used. For example, numerous articles may report on data from the same registry. In cases where the articles reported on different data collection years or subgroups (gender, age), all data (every article) were included. Demographic data were recorded, including age, gender, and study location. Diagnostic data were collected, as were the sources of those data and definitions/diagnostic criteria for brain tumors. Incidence and prevalence estimates of brain tumors from each study were recorded, along with any stratification by age, gender, or year of data collection.

### Data Quality

The quality of the included studies was evaluated independently by 2 reviewers, using an assessment tool (Supplementary Appendix B) that was developed based on a previous study quality scoring system and published guidelines.<sup>5,6</sup> The quality tool assessed sample representativeness, condition assessment, and statistical methods. Each study was assigned a quality score of 0 to 8 based on fulfillment of the quality criteria.

### Data Synthesis and Analysis

To assess for significant between-study heterogeneity, the Cochran Q statistic was calculated and  $I^2$  was used to quantify the magnitude of between-study heterogeneity. It was decided *a priori* that statistically significant heterogeneity (Q statistic  $P$ -value  $< .05$ ) was absent the pooled estimate and 95% confidence intervals would be calculated using a fixed-effect model. If significant heterogeneity was present, a random-effects model was used. Publication bias was investigated visually using funnel plots and statistically using Begg's and Egger's tests.

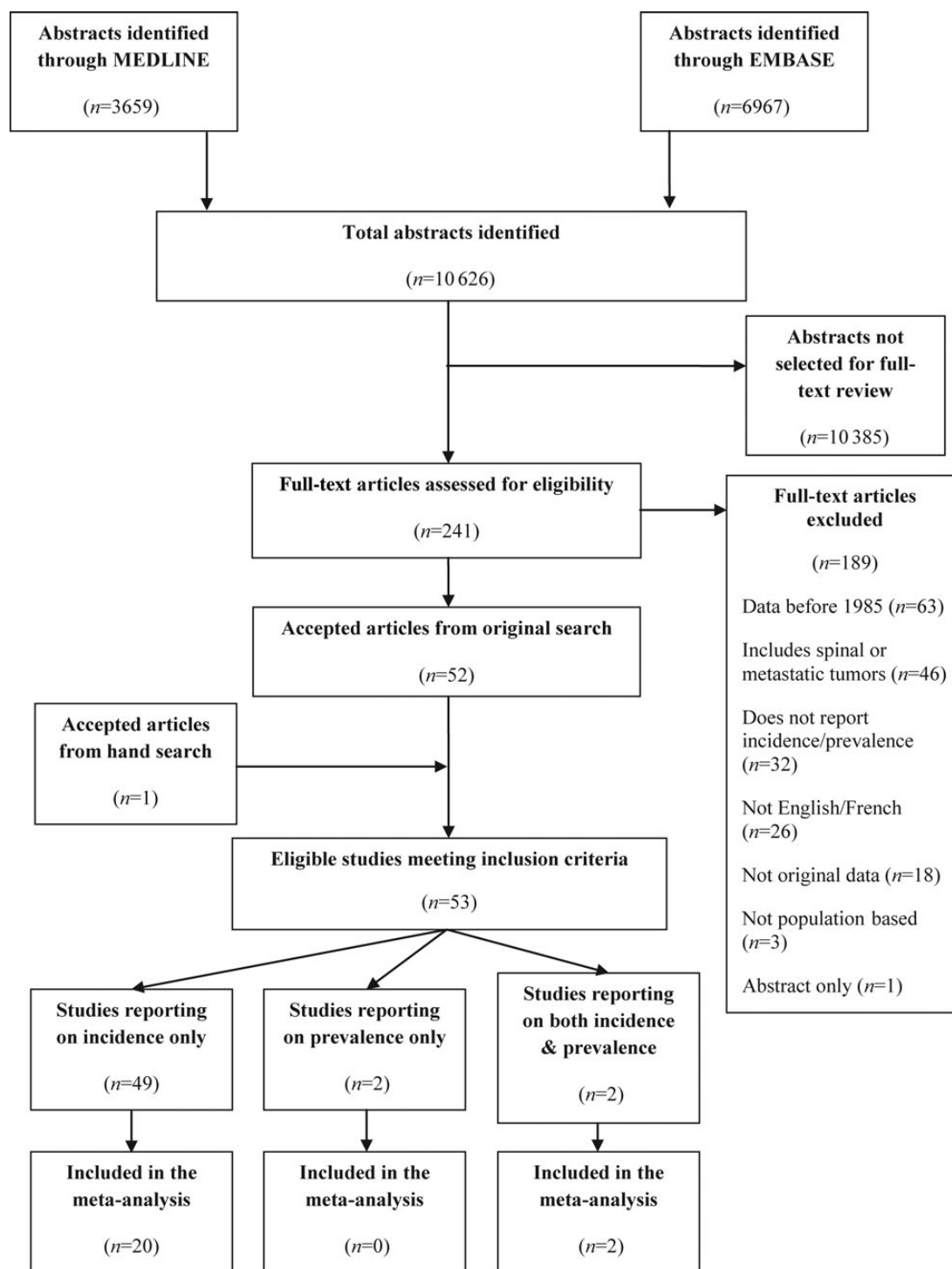
For all tests,  $P < .05$  was deemed to be significant. All statistical analyses were carried out in R version 2.14. The "meta" package was used to produce the pooled estimates, forest plots, and publication bias assessment. The "metafor" package was used to conduct the meta-regression using restricted maximum likelihood estimation.

## Results

### Identification and Description of Studies

The results of the search strategy yielded a total of 10 626 citations: 3659 from Medline and 6967 from Embase, some of which were duplicates (Fig. 1). After the initial screen, 241 articles met the criteria for full-text review, of which 189 were excluded (63 reported data before 1985, 46 included spinal or metastatic tumors, 32 did not report on the incidence or prevalence of brain tumors, 26 were not in English/French, 18 were not original data, 3 were not population based, and 1 was only an abstract). Hand-searching resulted in the inclusion of 1 additional article. From the 53 eligible studies overall (original search + hand-searching), 22 were included in the meta-analysis; the 16 articles reporting on the incidence proportion of all primary brain tumors were deemed too clinically heterogeneous to pool (1 was included in the incidence rate analyses), there were too few studies reporting on the point ( $n = 2$ ) and period ( $n = 2$ ) prevalence estimates to pool (however, these were pooled in the incidence rate analyses), and for the remaining incidence rate articles, 14 were not pooled (12 provided only age-standardized or adjusted estimates, and 2 provided only the estimate, with no confidence intervals or cases). Characteristics of the 53 included studies (reporting on all malignant and nonmalignant primary brain tumors) are shown in Table 1 and Supplementary Tables S1–S11.

Of the 53 included studies, 2 reported on the prevalence of brain tumors,<sup>7,8</sup> 49 reported on the incidence of brain tumors,<sup>9–57</sup> and 2 reported on both the incidence and prevalence of brain tumors.<sup>58,59</sup> Twenty-nine of the studies reported on



**Fig. 1.** Brain tumor systematic review study flow diagram.

data from Europe, 14 from North America, 7 from Asia, 2 from Australia, 1 from Africa, and 0 from South America (some studies report on data from more than one country).

Twenty studies reported on all brain tumors, 15 on gliomas, 28 on medulloblastomas/primitive neuroectodermal tumors

(PNETs), 8 on pineal gland tumors, 12 on nerve sheath tumors, 5 on germ cell tumors, 18 on sellar tumors, 2 on hemangioblastomas, 7 on other tumors, 14 on meningiomas, 7 on primary central nervous system lymphomas, and 4 on choroid plexus tumors.

**Table 1.** Prevalence studies of brain tumors

Study, Date, Reference	Region	Population	Diagnostic Criteria	Data Source	Diagnosis Established by	Tumor Type	Prevalence Date	Overall Prevalence (95% CI)
Daly, 2006 <sup>7</sup>	Belgium	All ages	Unspecified	Hospital clinic review	Histology; hormonal workup	Pituitary adenoma	September 30, 2005	94 (72.2–115.8) per 100 000
Davis, 2001 <sup>20</sup>	United States	All ages	ICD-O; WHO	Registry	Behavior codes; histology	Benign brain; malignant brain; primary brain	1985–1989	97.5 per 100 000 (NA); 29.5 per 100 000 (NA); 130.8 (NA) per 100 000
Fernandez, 2010 <sup>8</sup>	Banbury, Oxfordshire, England	All ages	ICD-O	Administrative database	Histology; hormonal workup	Pituitary adenoma	July 31, 2006	77.6 (NA) per 100 000
Porter, 2010 <sup>59</sup>	United States	All ages	ICD-O; ICD-O-1	Registry	Histology	Primary brain; glioma; meningioma	2004, 2005	221.8 (NA) per 100 000; 6.0 per 100 000; 6.0 per 100 000

Abbreviations: ICD-O, International Classification of Diseases for Oncology; WHO, World Health Organization classification of brain tumors; NA, not available.

### Prevalence of Brain Tumors

Table 1 lists all the prevalence studies of primary brain tumors identified in this review. Two eligible articles reported on the *point prevalence* of brain tumors but were not included in a meta-analysis, as only overall brain tumors were analyzed. One study reported a point prevalence of pituitary adenoma of 94 per 100 000,<sup>7</sup> and the other study reported a point prevalence of pituitary adenoma of 77.6 per 100 000.<sup>8</sup>

Two eligible articles reported on the *period prevalence* of brain tumors but were not included in a meta-analysis, as they reported on different types of tumors and only overall brain tumors were analyzed. The total number of participants included was not reported in either paper. One study reported period prevalences of all primary brain tumors of 221.8 per 100 000, gliomas of 6.0 per 100 000, and meningiomas of 6.0 per 100 000.<sup>59</sup> The other study of period prevalence reported an estimate of 130.8 per 100 000 for all primary brain tumor types.<sup>20</sup>

### Incidence of Brain Tumors

Supplementary Tables S1–S11 list all of the incidence studies of primary brain tumors identified in this review. Sixteen studies<sup>11–15,17,18,48–51,53–57</sup> reported an incidence proportion of brain tumors but were too heterogeneous to be included in a meta-analysis. Five studies reported on all primary brain tumors, 8 on medulloblastomas/PNETs, 3 on gliomas, 3 on sellar tumors, 2 on germ cell tumors, 2 on CNS lymphomas, 2 on pineal tumors, 1 on choroid plexus tumors, 1 on meningiomas, 1 on nerve sheath tumors, and 1 on other tumor types, while some studies reported on multiple tumor types. The incidence proportion estimates ranged from 0.051 per 100 000 (germ cell tumors)<sup>50</sup> to 25.48 per 100 000 (all primary brain tumors).<sup>17</sup>

Twenty-two studies of the 36 identified studies that reported an incidence rate<sup>9,10,16,19–47,52,54–59</sup> met all eligibility criteria for inclusion in a meta-analysis of the overall incidence rate of brain tumors. A random-effects model found the overall incidence rate on all primary brain tumors to be 10.82 (95% CI: 8.63–13.56) per 100 000 person-years (Supplementary Fig. S1). The incidence rate estimates ranged from 0.01 per 100 000 person-years (pineal tumors)<sup>34</sup> to 25.95 per 100 000 person-years (all primary brain tumors). Significant heterogeneity existed between most estimates.

### Sources of Heterogeneity

#### Gender

The overall incidence rate of all primary brain tumors was 15.80 per 100 000 person-years (95% CI: 10.30–24.24) in females (Supplementary Fig. S2) and 14.33 per 100 000 person-years (95% CI: 10.07–20.38) in males (Supplementary Fig. S3). Meta-regression including gender in the model showed no statistically significant difference by gender on the overall estimate of brain tumors ( $P > .05$ ). The pooled incidence rate of all meningiomas by gender was borderline significant ( $P = .05$ ), with the estimate for females (4.21 per 100 000 person-years [95% CI: 2.52–7.04]) being higher than that for males, 2.33 (1.35 per 100 000 person-years [95% CI: 1.35–4.01]). There

were no other significant differences by gender for other tumor subtypes (Supplementary Table S13).

### Age

The incidence rate of medulloblastomas was significantly higher in children (0.49 per 100 000 person-years [95% CI: 0.42–0.66]) than adults (0.05 per 100 000 person-years [95% CI: 0.03–0.10]<sup>27</sup>),  $P < .05$ , while the incidence rate for all gliomas was higher in adults (14.07 per 100 000 person-years [95% CI: 11.98–16.52]) than in children (0.18 per 100 000 person-years [94% CI: 0.10–0.33]),  $P < .05$ . Unfortunately, there were insufficient data to compare the incidence rate of other brain tumor types by age.

### Time

Using the study data collection start year, midyear, and end-year (separately) as continuous factors, changes in the incidence rate of all brain tumors were assessed over time using meta-regression. The meta-regression revealed no statistically significant changes in the incidence rate of all brain tumors over time, using the data collection start year ( $P = .72$ ), midyear ( $P = .53$ ), or end year ( $P = .46$ ).

### Publication Bias

For the incidence rate of brain tumors overall, there was no statistically significant evidence of publication bias for Begg's ( $P > .05$ ) and Egger's tests ( $P > .05$ ); however, upon visual inspection there was slight asymmetry in the funnel plot. Evidence of publication bias was not found for the incidence proportion of brain tumors using Egger's and Begg's test ( $P > .05$ ); however, the funnel plot also showed slight asymmetry. There was not a sufficient sample size to conduct publication bias analyses for the point and period prevalence of brain tumors.

### Study Quality

The median study quality score for studies reporting on the incidence or prevalence of brain tumors was 4/8 (range 2–7). All studies described the target population in detail and either sampled the entire population or used probability sampling (Supplementary Table S12). Thirty-three studies reported a response rate  $>70\%$ , and of those, 7 articles adequately described the nonresponders. Although population based, the majority of studies did not specifically report on whether their sample was representative of the target population (19/53). Most (32) studies used standardized data collection methods; however, only 7 reported using validated criteria to assess for the presence of brain tumors. Finally, fewer than half of the studies (20) reported estimates with their accompanying confidence intervals or by subgroups.

## Discussion

Through a systematic review of the latest literature, we are able to provide pooled estimates of the incidence of different types of primary brain tumors. The overall pooled incidence rate of

primary brain tumors was found to be 10.82 per 100 000 person-years. Estimates of incidence rates ranged from 0.01 per 100 000 person-years (pineal tumors) to 25.95 per 100 000 person-years (all primary brain tumors).

The heterogeneous incidence estimates found in our review likely reflect in part the fact that primary brain tumors are a heterogeneous group of disease. This heterogeneity creates difficulties when reporting the epidemiology of overall brain tumors, as reflected in the wide range of incidence estimates found even within studies examining similar tumor types. The differences in incidence estimates can also be a reflection of differences in reporting cases to cancer registries or to the lack of accurate case ascertainment, based on variable diagnostic capabilities of each center or region. In addition, variations in incidence estimates may be due to diverse study methodologies. As an example, Porter et al<sup>59</sup> included only tumors with available pathological diagnosis and reported an incidence rate of 6 per 100 000 person-years for all gliomas, while Elia-Pasquet et al<sup>23</sup> included tumors whether or not confirmed histologically and reported an incidence rate of 14.07 per 100 000 person-years for all gliomas.

In our review, there was one borderline significant difference in the incidence rate of primary brain tumors according to gender. The incidence rate of meningiomas in females was close to being significantly higher than the incidence rate in males ( $P = .05$ ). When reviewing rate differences according to age, the data were limited. Only the incidence rates of medulloblastomas and of all gliomas were amenable to age-stratified analysis. In our meta-analysis, the incidence rate of medulloblastomas in children was 0.49 per 100 000 person-years, while Giordana et al<sup>27</sup> reported it in adults to be 0.05 per 100 000 person-years. Since Giordana et al included only histologically confirmed tumors and the pediatric papers also included a small percentage of nonhistologically confirmed tumors, these differences need to be interpreted cautiously. Unfortunately, there were insufficient data to conduct a meta-analysis of the prevalence of overall primary brain tumors.

The only previous systematic review on the worldwide epidemiology of brain tumors was published in 1998<sup>3</sup>; of the 20 included articles, 17 were either published or collected data from before 1985, an exclusion criterion for the current study. The remaining 3 articles published after this time were included in our review,<sup>19,31,54</sup> resulting in a total of 50 new articles included in the present study. In the earlier systematic review, the incidence rate of all primary tumors ranged from 4.3 to 18.6 per 100 000 persons per year, a finding consistent with our current study, where we report a pooled incidence rate of 10.82 per 100 000 persons per year.<sup>3</sup> More recently, a systematic review of the epidemiology of brain tumors in Iran was published, and included 9 articles from that country.<sup>60</sup> None of the 9 articles included in the Iranian review were included in the present study, as they were not population based according to our prespecified criteria. The review of Iranian studies found an overall incidence rate of primary malignant brain tumors of 2.74 per 100 000 persons per year<sup>60</sup>; the lower number found in this study compared with our review may be the result of the inclusion of only malignant tumors in the primary analysis.

The worldwide review of brain tumor by Counsell and Grant<sup>3</sup> found no evidence of an increase in incidence rate over time, though they used only a dichotomous measure of time (data collection before or during/after the 1980s). We also found no evidence of an increase in the incidence rate of all brain tumors over time, using time as a continuous variable. It has been suggested that the increases reported in some studies over time are entirely artifactual, largely due to an increase in the recognition of brain tumors caused by the rise in the amount of CT scans conducted, an increase in the number of neurologists practicing in the field, and changes to coding practices worldwide.<sup>3</sup> As with the review by Counsell and Grant,<sup>3</sup> we found a higher incidence rate of medulloblastomas in children compared with adults. The significant differences between males and females in the incidence rate of most tumor types reported in both previous systematic reviews<sup>3,60</sup> were not replicated in the current study, which found only a slight gender difference in the incidence rate for meningiomas.

The evidence-based reporting on risk factors for brain tumors is mixed and is likely a reflection of the heterogeneity between tumor types.<sup>61,62</sup> Reproductive and hormonal factors have been associated with an increased risk of some tumor types; the risk of meningioma is almost double in women versus men.<sup>61</sup> Exposure to therapeutic doses of ionizing radiation is an established (and potentially modifiable) risk factor for some brain tumors, including pituitary adenoma, meningioma, and glioma.<sup>61</sup> Other potential risk factors for brain tumor include genetic factors, familial aggregation, and environmental exposures.<sup>61,62</sup> Though risk factors for brain tumor were not assessed in the current study, an understanding of them is essential for effective prevention and therapeutic strategies.

Our review has many strengths, including searching more than one bibliographical database (Medline and Embase), incorporating a quality assessment tool for each study, conducting a meta-analysis following a predetermined protocol and guidelines, and completing an assessment of study heterogeneity using a random-effects model. However, our review is not without limitations. We reviewed articles published in only English or French and we cannot rule out the possibility of publication bias, as there was slight asymmetry upon visual inspection of the funnel plot, although this did not reach statistical significance. Few studies reported gender- and/or sex-stratified estimates by tumor type, limiting our ability to calculate pooled estimates for these subgroups. In addition, the median quality score of the included studies was quite low, as many studies did not report estimates with confidence intervals or by subgroups and it was unclear how many used validated criteria to determine whether brain tumors were present. We do not believe this would have an impact on the results presented here, as those studies without confidence intervals would not be pooled. The majority of the study quality issues could be mitigated by more clear and accurate reporting by original study authors. Another limitation is the gap in knowledge regarding the prevalence of brain tumors internationally and by subtypes. Both prevalence and incidence data are needed to truly assess the global burden of brain tumors.

Based on our findings, we can conclude that there is a need to produce more accurate and comparable incidence and prevalence estimates of primary brain tumors across the world. A standardized approach to the study of the epidemiology of

these tumors is needed to better understand the burden of the disease and the possible geographical variations in the incidence. Future studies investigating the incidence or prevalence of brain tumors should adopt similar methodologies and use a standardized approach to case ascertainment.

## Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

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*Conflict of interest statement.* The authors have no conflicts of interest to disclose.

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