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Meta-Analysis

Birth Weight and Subsequent Risk of Childhood Primary Brain Tumors: A Meta-Analysis

Thomas Harder[1], Andreas Plagemann[1], and Anja Harder[2]

[1] Clinic of Obstetrics, Research Group "Experimental Obstetrics," Charité–Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany.
[2] Institute of Neuropathology, Charité–Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany.

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The etiology of primary brain tumors is largely unknown. Since a peak of incidence occurs during childhood, factors operating very early in life might play a key role. Previous studies have suggested that high birth weight is associated with an increased brain tumor risk. The authors conducted a meta-analysis on the association between birth weight and risk of specific histologic types of primary brain tumors. They included published studies (1966–2007) that reported odds ratios and 95% confidence intervals for brain tumors associated with birth weight. The authors identified eight studies involving 1,748,964 children, of whom 4,162 suffered from brain tumors of three histologic types (astrocytoma, medulloblastoma, and ependymoma). For astrocytoma, high birth weight (>4,000 g) was associated with increased risk (odds ratio = 1.38, 95% confidence interval (CI): 1.07, 1.79), with each 1,000-g increase in birth weight being associated with a 19% (95% CI: 4, 36) increase in risk. For medulloblastoma, high birth weight was also positively associated with increased risk (odds ratio = 1.27, 95% CI: 1.02, 1.60). No association was found for ependymoma. These findings indicate that birth weight is related to the development of childhood brain tumors, with high birth weight being a risk factor for the two most common types of brain tumors.

birth weight; brain neoplasms; child; meta-analysis

Abbreviations: CI, confidence interval; IGF-1, insulin-like growth factor 1; OR, odds ratio.

Although detailed knowledge on molecular mechanisms acting in brain tumors has been accumulated over the past several years, the etiology of primary brain tumors remains one of the most prominent challenges for cancer research. Besides ionizing radiation and genetic syndromes like neurofibromatosis and Li-Fraumeni syndrome, clear-cut risk factors have not been identified so far (for reviews, see Savitz and Trichopoulos (1) and Baldwin and Preston-Martin (2)). Especially for the most common primary brain tumors, astrocytoma and medulloblastoma/primitive neuroectodermal tumors, a peak of incidence occurs during childhood (3), which consequently leads to the hypothesis that risk factors operating very early in life might play a decisive role in the etiopathogenesis of these tumors. Supportingly, some studies exist which indicate that prenatal or early postnatal exposures, like exposure to *N*-nitrosoamines, might increase the risk of developing brain tumors during childhood (for a review, see Baldwin and Preston-Martin (2)). However, the current evidence is limited, at least partly because prenatal and perinatal exposures are difficult to assess accurately, especially retrospectively.

Birth weight has often been suggested to be a crude but easily accessible marker of prenatal exposures. Only a small proportion of birth weight is attributable to genetic influences; most of its variance is determined by nongenetic factors, such as maternal nutritional status and body weight, maternal diseases, and environmental exposures during pregnancy (4). Remarkably, nearly 30 years ago, Gold et al. (5) had already

Correspondence to Dr. Thomas Harder, Clinic of Obstetrics, Research Group "Experimental Obstetrics," Charité–Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany (e-mail: thomas.harder@charite.de).

observed that children with brain tumors had higher birth weights than controls. However, conflicting results have been published subsequently. While Savitz and Ananth (6) confirmed the early findings of Gold et al., Preston-Martin et al. (7) found no association. Interpretation of these earlier findings is largely complicated by the fact that brain tumors occur in a diverse array of histologic types, with little clarity regarding the extent to which they share etiology (1).

Therefore, we aimed to summarize the currently published literature on this issue. We performed a comprehensive meta-analysis on the relation between birth weight and risk of subsequent brain cancer, with particular emphasis on the histologic type of the tumor.

MATERIALS AND METHODS

Study base

We performed a comprehensive literature search according to the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines for meta-analyses of observational studies (8), including the databases MEDLINE (1966–2007) and EMBASE (1989–2007), to identify studies that investigated the relation between birth weight and risk of primary brain tumors. The complete literature search strategy is outlined in the Web Appendix, which is posted on the *Journal*'s website (http://aje.oxfordjournals.org/), and covered all major histologic subtypes of primary brain tumors. The entire search was performed with the full-text option, without language restrictions. Furthermore, we manually searched all references cited in original studies and reviews.

To be eligible, a study had to fulfill the following criteria, defined a priori: 1) It had to be an original report on the relation between birth weight and risk of histologically specified primary brain tumors, and 2) odds ratios and 95 percent confidence intervals (or data with which to calculate them) for risk of brain tumors in at least two strata of birth weight had to have been presented. Alternatively, an odds ratio and 95 percent confidence interval for the change in primary brain tumor risk per unit of change in birth weight had to have been reported. Only studies that specified the histologic type(s) of primary brain tumor(s) were included. The course of the systematic literature review is illustrated in figure 1.

Data abstraction

From all studies included, data were abstracted in duplicate, using a standardized form. The following study characteristics were extracted: publication year, country, study design, year of birth, age at diagnosis, study size, matching ratio (if a case-control study), matching variables (if a case-control study), source of controls (if a case-control study), confounding factors considered, source of case diagnosis, source of data for birth weight, unadjusted effect measure, adjusted effect measure, and confounders. An independent reviewer confirmed all data entries.

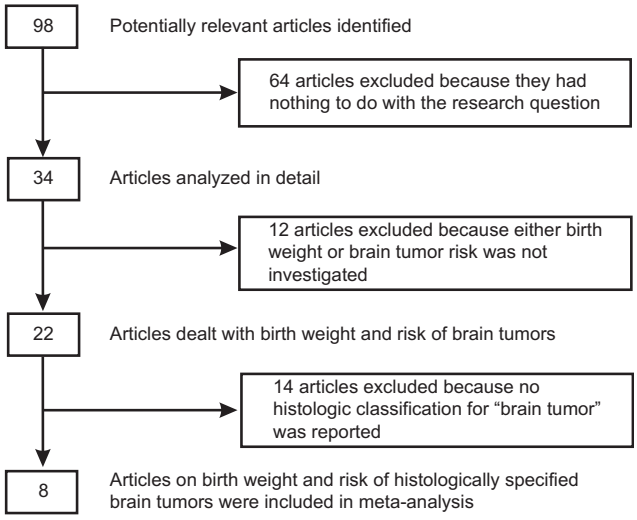

FIGURE 1. Course of a systematic literature review on birth weight and risk of childhood primary brain tumors, 1966–2007.

Statistical analysis

Three different meta-analytic approaches were used: 1) A birth weight cutoff of 4,000 g (high birth weight) (9) was used to compare risks of specific brain tumors above and below this value (dichotomous comparison); 2) the dichotomous approach was repeated for a birth weight cutoff of 2,500 g (low birth weight) (9); and 3) the pool-first method (10) was used to combine regression coefficients obtained from the studies for a linear trend analysis.

Dichotomous comparisons. We extracted data on numbers of subjects with and without specific brain tumors above or below the cutoff value and calculated corresponding crude odds ratios and 95 percent confidence intervals. We constructed both fixed-effects and random-effects models to estimate the pooled odds ratios for risk of the specific histologic type of brain tumor above versus below the respective cutoff value across all studies.

Linear trend analysis. For studies that provided data for more than two categories of birth weight, we applied the ''pool-first method'' to quantify the dose-response relation between birth weight and risk of primary brain tumors. After visual inspection of the plots to ascertain model adequacy, we calculated a study-specific regression coefficient and corresponding 95 percent confidence interval for each study using a log-linear model. After exponentiation, the resulting odds ratios and 95 percent confidence intervals for change in risk per 1,000-g increase in birth weight were pooled using a random-effects model (10).

Assessment of heterogeneity. The heterogeneity of study results was assessed by means of a Cochrane's Q-based test.

Influence analysis. The robustness of the pooled estimate was checked by influence analysis, using a random-effects model. Each of the study estimates was individually omitted from the data set, followed in each case by recalculation of the pooled estimate of the remaining studies.

Publication bias. Publication bias was assessed by inspection of the funnel plot and by formal testing for funnel plot asymmetry using Begg's test and Egger's test.

Software. All calculations were performed using STATA, version 8 (Stata Corporation, College Station, Texas).

RESULTS

Study characteristics

As figure 1 shows, eight studies were identified for inclusion in the meta-analysis. Investigators in these studies provided results on three histologically different primary brain tumors: Eight of the studies gave data on astrocytoma, seven studies gave data on medulloblastoma/primitive neuroectodermal tumors, and four gave data on ependymoma (11–18). We could not identify any study in which investigators reported on any other histologic type of primary brain tumor. Fourteen studies had to be excluded because the histologic type of brain tumor was not specified (5–7, 19–29).

The characteristics of the included studies are displayed in table 1. The studies involved a total of 1,748,964 persons, of whom 4,162 suffered from one of the three types of primary brain tumors. Study size ranged from 326 probands to 1,489,297 probands. Two of the studies were cohort studies, while the remaining six had a case-control design, with matching ratios ranging from 1:1 to 1:5. The first study was published in 1990, while the most recent appeared in 2003. The studies were performed in 10 countries located on four continents, including one study (15) which was a multicenter study conducted in seven countries. In all eight studies, cases were derived from cancer registries.

Birth weight and risk of astrocytoma

High birth weight. All eight studies in which investigators reported on astrocytoma provided data for calculation of odds ratios and 95 percent confidence intervals for astrocytoma risk in subjects with high birth weights (>4,000 g) as compared with those below this cutoff value. Figure 2, part *A*, shows a forest plot with odds ratios and 95 percent confidence intervals and the pooled estimate for risk of astrocytoma in subjects with high birth weights. High birth weight was associated with increased risk of astrocytoma. This effect was observed using both the random-effects model (odds ratio (OR) = 1.38, 95 percent confidence interval (CI): 1.07, 1.79) and the fixed-effects model (OR = 1.36, 95 percent CI: 1.17, 1.59).

According to Cochrane's Q statistic, study results were significantly heterogeneous ($p = 0.02$). Influence analysis (random-effects model) showed that the pooled estimate was robust: Omission of individual study estimates led to pooled odds ratios ranging from 1.32 (95 percent CI: 1.0, 1.76) to 1.47 (95 percent CI: 1.26, 1.73). We additionally evaluated whether the result differed according to study design. Cohort studies showed nearly the same effect size (OR = 1.36, 95 percent CI: 0.22, 8.15) as case-control studies (OR = 1.45, 95 percent CI: 1.23, 1.70), although the former was not significant. No indication of publication bias was found, as investigated by visual inspection of the funnel plots (not shown) and nonsignificant Begg's ($p = 0.39$) and Egger's ($p = 0.63$) tests.

Low birth weight. In six out of the eight studies, investigators gave data for calculation of odds ratios and 95 percent confidence intervals for astrocytoma risk in subjects with low birth weight (<2,500 g) as compared with those above this cutoff value. Figure 2, part *B*, shows a forest plot with odds ratios and 95 percent confidence intervals and the pooled estimate for risk of astrocytoma associated with low birth weight. Low birth weight was related to a nonsignificantly decreased risk of astrocytoma in both the random-effects model (OR = 0.85, 95 percent CI: 0.58, 1.25) and the fixed-effects model (OR = 0.85, 95 percent CI: 0.64, 1.13).

Study results did not show significant heterogeneity ($p = 0.21$). No indication of publication bias was found, as investigated by visual inspection of the funnel plots (not shown) and nonsignificant Begg's ($p = 1.0$) and Egger's ($p = 0.91$) tests.

Linear trend analysis. Since the results of the dichotomous analyses pointed towards a linear positive relation between birth weight and risk of astrocytoma, we applied linear trend analysis to the data. From five of the studies, we were able to calculate an odds ratio and 95 percent confidence interval for risk of astrocytoma per 1,000-g linear increase in birth weight. Each 1,000-g increase in birth weight was found to be associated with a 19 percent (95 percent CI: 4, 36) increase in risk of astrocytoma. Results were not significantly heterogeneous ($p = 0.19$).

Birth weight and risk of medulloblastoma

High birth weight. In seven studies, investigators gave data for calculation of odds ratios and 95 percent confidence intervals for risk of medulloblastoma in subjects with high birth weight. As figure 3, part *A*, shows, high birth weight was associated with increased risk of medulloblastoma. The result in the random-effects model (OR = 1.27, 95 percent CI: 1.02, 1.60) was nearly identical to that obtained using the fixed-effects model (OR = 1.28, 95 percent CI: 1.03, 1.58).

Study results did not show significant heterogeneity ($p = 0.37$). Influence analysis (random-effects model) showed robustness of the pooled estimate: Omission of individual study estimates led to pooled odds ratios ranging from 1.21 (95 percent CI: 0.90, 1.62) to 1.37 (95 percent CI: 1.09, 1.72). Cohort studies showed a greater effect size (OR = 1.85, 95 percent CI: 1.01, 3.38) than did case-control studies (OR = 1.20, 95 percent CI: 0.95, 1.53). No indication of publication bias was found, as investigated by visual inspection of the funnel plots (not shown) and nonsignificant Begg's ($p = 0.55$) and Egger's ($p = 0.83$) tests.

Low birth weight. Five of the seven studies on medulloblastoma reported data for calculation of odds ratios and 95 percent confidence intervals for tumor risk in subjects with low birth weight (<2,500 g) as compared with those above this cutoff value. As figure 3, part *B*, shows, low birth weight was associated with a nonsignificantly increased risk of medulloblastoma (OR = 1.64, 95 percent CI: 0.42, 6.48); however, the 95 percent confidence interval was fairly wide.

TABLE 1. Characteristics of eight studies included in a meta-analysis of birth weight and risk of childhood primary brain tumors, 1966–2007*

Authors and year (ref. no.)	Country (ies)	Study design	Probands' years of birth	Age (years) at diagnosis	Final study size (no. of probands)	No. of cases	No. of controls	Matching variables (if case-control study)	Source of controls (if case-control study)	Confounding factors considered (if cohort study)	Source of case diagnosis	Source of data for birth weight	Data on astrocytoma	Data on medulloblastoma	Data on ependymoma
Emerson et al., 1991 (11)	United States	Case-control	1965–1986	<11	942	157	785	Year of birth, place of birth	Random population-based sample	NA†	Tumor registry	Vital records	X	X	X
Heuch et al., 1998 (12)	Norway	Cohort	1967–1992	<16	1,489,297	459	NA†	NA	NA	Sex, age	Cancer registry	National Medical Birth Registry	X	X	
Kuijten et al., 1990 (13)	United States	Case-control	1965–1986	<15	326	163	163	Age, ethnicity	Random digit dialing	NA	Tumor registry	Interview	X		
Linet et al., 1996 (14)	Sweden	Case-control	1973–1989	<15	3,420	570	2,850	Sex, date of birth	Random sample from birth registry	NA	Cancer registry	Birth registry	X	X	X
McCredie et al., 1999 (15)	Australia, Canada, Spain, United States, Israel, France, and Italy	Case-control	1958–1994	<19	3,441	1,218	2,223	Sex, age	Random digit dialing, registries	NA	Cancer registry, hospital records	Interview	X	X	
Mogren et al., 2003 (16)	Sweden	Cohort	1955–1990	NR	248,701	237	NA	NA	NA	Sex, age	Cancer registry	Birth registry	X	X	X
Schüz et al., 2001 (17)	Germany	Case-control‡	1975–1994	<15	599	115 and 497	230 and 497	Sex, age, location	Local population	NA	Cancer registry	Questionnaires, interviews	X	X	X
Von Behren and Reynolds, 2003 (18)	United States	Case-control	1983–1997	<5	2,238	746	1,492	Sex, date of birth	Local population	NA	Cancer registry	Birth certificates	X	X	

* All studies included both males and females.
† NA, not applicable.
‡ Combined analysis of two studies.

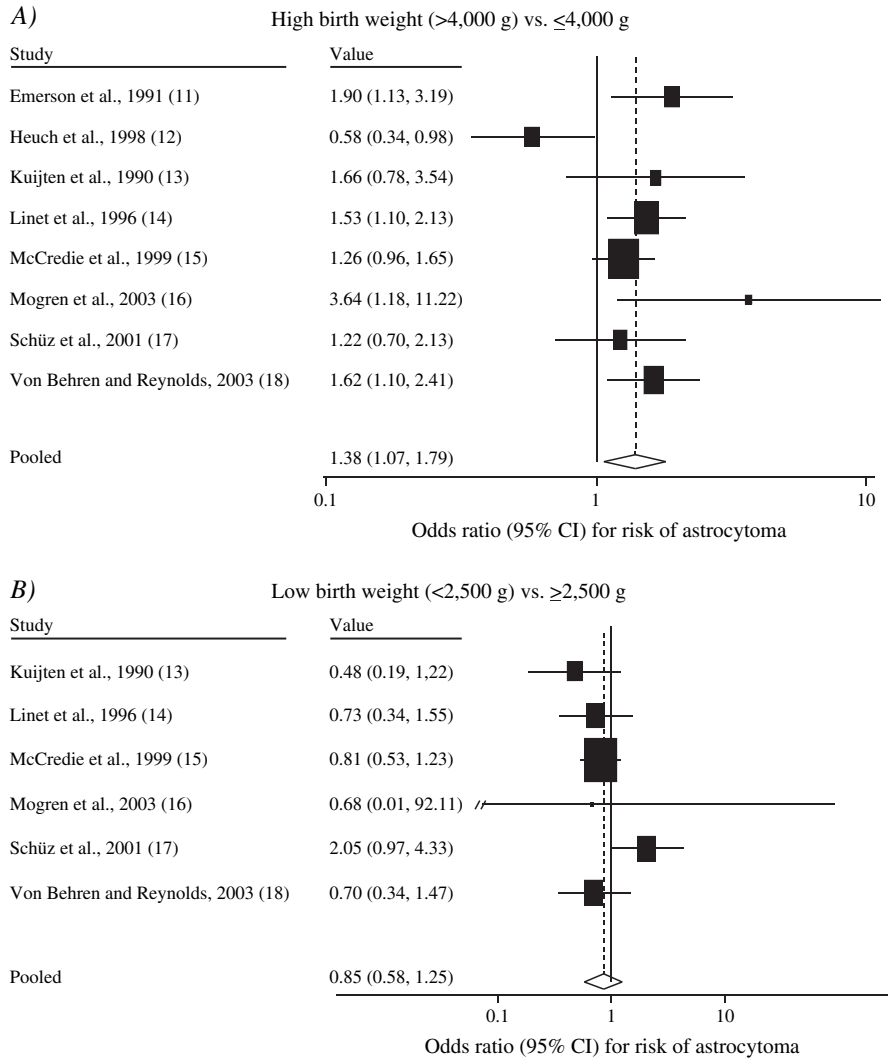

FIGURE 2. Odds ratios for astrocytoma in subjects with high birth weight (>4,000 g) (part *A*) and low birth weight (<2,500 g) (part *B*) in a meta-analysis, 1966–2007. Studies are ordered alphabetically by first author. The pooled odds ratios (diamonds) were calculated by means of a random-effects model. Ninety-five percent confidence intervals (CIs) are shown in parentheses and as horizontal bars.

The effect was more pronounced in the fixed-effects model (OR = 2.1, 95 percent CI: 1.42, 3.10).

Significant heterogeneity was observed ($p < 0.001$). Furthermore, the effect size was largely influenced by one study: Omission of the report by Von Behren and Reynolds (18) lowered the pooled odds ratio to 1.04 (95 percent CI: 0.66, 1.65). Neither inspection of the funnel plots (not shown) nor Begg's test ($p = 0.81$) nor Egger's test ($p = 0.81$) gave an indication of publication bias.

Since these data indicated the existence of a nonlinear relation between birth weight and risk of medulloblastoma, no trend analysis was performed.

Birth weight and risk of ependymoma

In only four out of the eight studies in the meta-analysis did investigators give data on risk of ependymoma according to birth weight. Although this was a small number of studies, we calculated pooled odds ratios and 95 percent confidence intervals for high and low birth weight, using a random-effects model. Neither for high birth weight (OR = 1.15, 95 percent CI: 0.65, 2.04) nor for low birth weight (OR = 1.65, 95 percent CI: 0.60, 4.53) was a clear relation with risk of ependymoma observed.

DISCUSSION

During recent years, a substantial number of published studies have indicated that birth weight is associated with risk of different types of cancer in later life, like breast cancer (30) and childhood leukemia (31). Regarding brain tumors, however, the evidence has appeared to be inconclusive. Our meta-analysis shows that for the two most common types of brain tumors in childhood, astrocytoma and

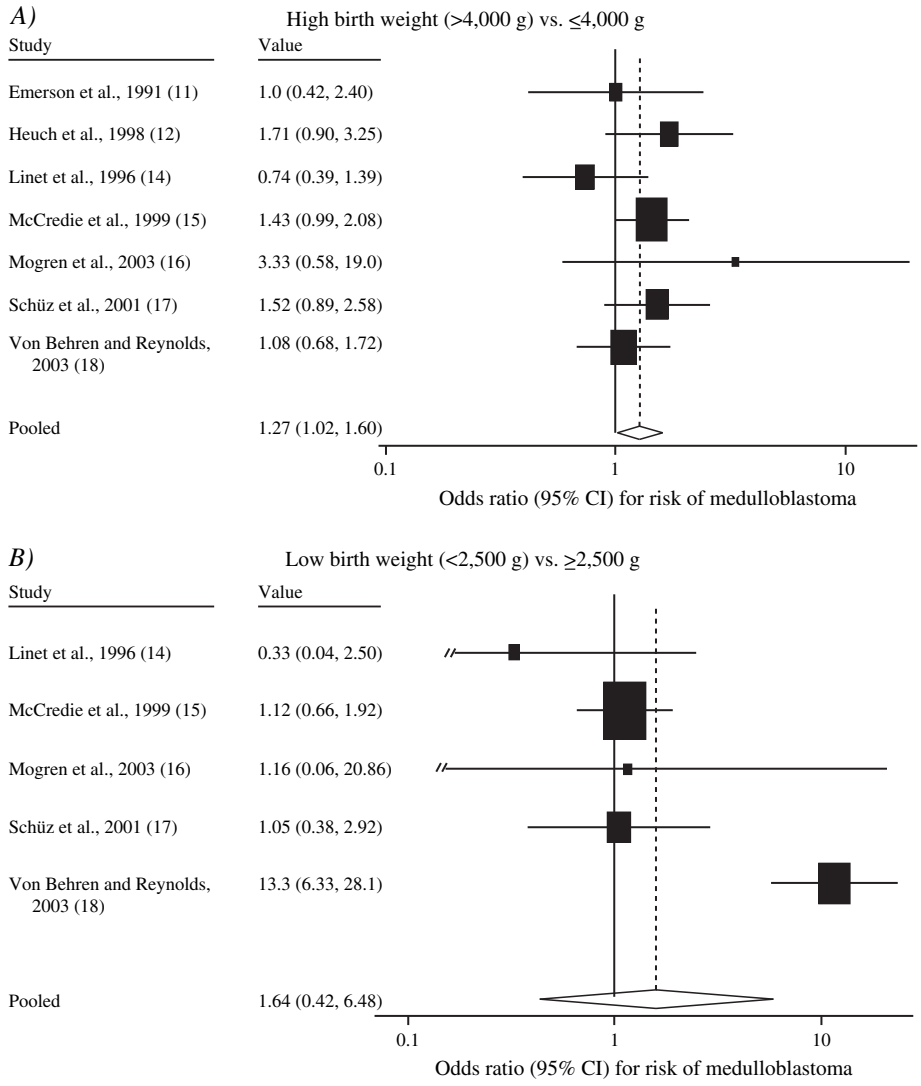

FIGURE 3. Odds ratios for medulloblastoma in subjects with high birth weight (>4,000 g) (part *A*) and low birth weight (<2,500 g) (part *B*) in a meta-analysis, 1966–2007. Studies are ordered alphabetically by first author. The pooled odds ratios (diamonds) were calculated by means of a random-effects model. Ninety-five percent confidence intervals (CIs) are shown in parentheses and as horizontal bars.

medulloblastoma/primitive neuroectodermal tumors, high birth weight is followed by a significantly increased risk of a brain tumor. Furthermore, in the case of astrocytoma, birth weight appears to be linearly positively related to later tumor risk: The higher the birth weight, the higher was the risk of astrocytoma. For both types of brain tumors, we did not find a significant association with low birth weight. In ependymoma, no relation between birth weight and tumor risk was observed, but the number of published studies was small.

Older studies, in particular, have produced inconclusive results on the relation between birth weight and brain tumor risk. This could be due to the fact that investigators in many of these studies did not consider brain tumors by histologic type but rather calculated an overall risk estimate. Consequently, depending on the frequency distributions of various histologic types of tumors in their samples, the authors might or might not have observed associations with high and low birth weight, respectively. Accordingly, during our systematic review, we excluded 14 studies that did not specify the histologic type of brain tumor, all having a case-control design. In nine of them (7, 19, 21–25, 28, 29), no relation between birth weight and tumor risk was observed. In two studies, high birth weight was associated with increased risk (5, 20). Remarkably, both studies were not restricted to children but also included adolescents (5) and adults (20). In three further studies (6, 26, 27), all performed in children under 15 years of age, both high and low birth weight were followed by increased brain tumor risk.

One limitation of the current literature quantitatively summarized here is that the studies included data only on children and adolescents (with the exception of one study (16) in which no clear age limit was reported). Therefore, it

is impossible to draw any conclusion regarding a relation between birth weight and brain tumor risk in adulthood, where the incidence of some types of primary brain tumors, like astrocytoma, has a second peak (32).

Studies on relations between perinatal risk factors and later outcomes are prone to confounding in multiple ways. Adjustment for confounders was performed in all of the case-control studies by matching. In general, controls were matched to cases on at least two factors, mostly age (or date of birth) and sex. Similarly, in both cohort studies, estimates were adjusted for sex and age. Adjustment for sex ensures that the associations observed can be explained neither by differences in mean birth weight between males and females nor by sex differences in the incidence and stage of the brain tumors investigated (1). However, in none of the studies had further adjustments been made. In particular, in none of the studies had birth weight been adjusted for gestational age, leaving open the possibility that the associations observed might also have had something to do with the degree of maturity of the child at birth.

In general, recall bias is a major issue in case-control studies on risk factors for brain cancer, mainly because patients with brain tumors might already have cognitive deficits which might limit their ability to correctly recall past exposures (1). However, it is unlikely that recall bias played a role in the studies included in this meta-analysis, because in the majority of the studies, birth weight data were derived from registries or clinical records. Furthermore, in those studies that used interview-based birth weight data, interviews were performed with the mother of the affected patient. Several studies have suggested that maternal recall of a baby's birth weight is highly accurate (33, 34).

In the nonregistry studies, selection bias could have played a role when response rates differed between cases and controls. However, in the only study included in this meta-analysis that used nonregistry data (15), nonparticipation rates did not differ greatly between cases (14 percent) and controls (13 percent).

In the analysis of astrocytoma, we observed significant heterogeneity between the study results. Astrocytoma can be further subdivided into at least four major histopathologic entities. Since it appears possible that the effect size varies according to histologic subtype, heterogeneity might result from the composition of the samples in the studies combined here for analysis. This idea is supported by the findings of Linet et al. (14); in their study, the relation to high birth weight was stronger in cases of high-grade astrocytoma, including glioblastoma, than in cases of low-grade astrocytoma. Consequently, further studies using established histologic classification systems for astrocytoma are needed to evaluate whether the association with high birth weight might be particularly strong for some histologic subtypes of this tumor.

A key question for interpretation of the results of our meta-analysis is which etiopathogenic mechanisms might be responsible for the observed associations. Astrocytomas are known to account for approximately 50 percent of childhood brain tumors, while medulloblastomas/primitive neuroectodermal tumors account for approximately 20 percent (35). Remarkably, for both of these types of childhood brain cancer—the two most common types—high birth weight was significantly associated with increased tumor risk. Since birth weight is unlikely to be an etiopathogenic factor itself, it might be suggested that mechanisms which stimulate prenatal weight gain as well as act simultaneously as long-term carcinogens might be responsible for this association. Against the background of the literature, three different hypotheses should be suggested in this regard. Firstly, Gold et al. (5) suggested that high birth weight would be an indicator of a greater number of cells, resulting in more cell divisions, which would increase vulnerability to carcinogens. Secondly, Heuch et al. (12) suggested for medulloblastoma that excess prenatal nutrition, for which high birth weight is an important indicator, may interfere with the migration of granular neuronal cells, which starts at about 30 weeks' gestation. Incompletely migrated cells stay immature and might have increased neoplastic potential.

The third hypothesis, currently the most advanced, is related to the fact that one of the most important endocrine systems which stimulates body weight and growth, the insulin-like growth factor system, plays a key role in brain ontogenesis as well as carcinogenesis. Insulin-like growth factor 1 (IGF-1) is positively correlated with birth weight and also has the potential to stimulate proliferation of malignant cells in general (36). In addition, high levels of IGF-1 have been strongly suggested to be involved in brain tumor pathogenesis (37). IGF-1 is present in the fetal brain, decreases in postnatal life, and reappears in neoplastic development in astrocytoma (for a review, see Trojan et al. (37)). Furthermore, IGF-1 has been suggested to be involved in the pathogenesis of medulloblastoma (38). Consequently, the question arises as to which conditions increase birth weight and stimulate IGF-1. The most important cause of increased birth weight in terms of maternal diseases during pregnancy is diabetes, especially gestational diabetes (39). Unfortunately, so far no one has examined the prevalence of diabetes in mothers of patients with astrocytoma or medulloblastoma.

Several authors have discussed whether there has been an increase in the incidence of primary brain tumors in the general population (1, 2). If an association between high birth weight and brain cancer risk exists, this might offer a provocative explanation for this trend over time, since birth weight, as well as the incidence of high birth weight among babies, has been increasing continuously in the United States and Europe in recent years (40, 41). If these associations turned out to be causal, measures to decrease the risk of excessive fetal growth and high birth weight—such as screening for and treating gestational hyperglycemia and avoiding maternal overweight during pregnancy—would be one possible method of lowering the risk of brain tumors in children.

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