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Birth weight and other perinatal factors and childhood CNS tumors: A case–control study in California

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Abstract

Aims—We conducted a large registry-based study in California to investigate the association of perinatal factors and childhood CNS tumors, with analysis by tumor subtype.

Methods—We linked California cancer and birth registries to obtain information on 3308 cases and 3308 controls matched on age and sex. We examined the association of birth weight, gestational age, birth order, parental ages, maternal conditions during pregnancy, newborn abnormalities and the risk of childhood CNS tumors using conditional logistic regression, with adjustment for potential confounders.

Results—The odds ratio (OR) per 1000 g increase in birth weight was 1.11 (95% CI: 0.99–1.24) for total childhood CNS tumors, 1.17 (95% CI: 0.97–1.42) for astrocytoma and 1.28 (95% CI: 0.90–1.83) for medulloblastoma. Compared to average-for-gestational age, large-for-gestational age infants were at increased risk of glioma (OR= 1.86, 95% CI: 0.99–3.48), while small-for-gestational age infants were at increased risk of ependimoma (OR = 2.64, 95% CI: 1.10–6.30). Increased risk of childhood CNS tumors was observed for 5-year increase in maternal and paternal ages (OR = 1.06, 95% CI: 1.00–1.12 and 1.05, 95% CI: 1.00–1.10 respectively). Increased risk of astrocytoma was detected for 5-year increase in paternal age (OR= 1.08; 95% CI: 1.00–1.16) and increased risk of glioma for maternal age > 35 years old (OR = 1.87; 95% CI: 1.00–3.52). Maternal genital herpes during pregnancy was associated with a pronounced increase in risk of total CNS tumors (OR = 2.74; 95% CI: 1.16–6.51). Other (non-sexually transmitted) infections during pregnancy were associated with decreased risk of total CNS tumors (OR = 0.28, 95% CI: 0.09–0.85). Maternal blood/immune disorders during pregnancy were linked to increased risk of CNS tumors (OR = 2.28, 95% CI: 1.08–4.83) and medulloblastoma (OR = 7.13, 95% CI: 0.82–61.03). Newborn CNS abnormalities were also associated with high risk of childhood CNS tumors (OR = 4.08, 95% CI: 1.13–14.76).

Conclusions—Our results suggest that maternal genital herpes, blood and immunological disorders during pregnancy and newborn CNS abnormalities were associated with increased risk of CNS tumors. Maternal infections during pregnancy were associated with decreased risk of CNS tumors. Advanced maternal and paternal ages may be associated with a slightly increased risk of CNS tumors. Factors associated with CNS tumor subtypes varied by subtype, an indicator of different etiology for different subtypes.

Keywords

Childhood CNS tumors; Childhood brain tumors; Birth weight; Birth order; Parental age; Perinatal factors; Pregnancy complications; Newborn abnormalities

1. Introduction

Brain and central nervous system (CNS) cancers are the second most common malignancy in childhood after childhood leukemia and the most common of the solid tumors, making up 16.6–21% of all childhood cancers in the U.S. [1–3].

Very little is known about the etiology of primary CNS and brain tumors. Several maternal and perinatal characteristics are suspected risk factors for CNS tumors in children but evidence for most is limited or inconsistent. Some consistent findings have been reported for exposure to infections during pregnancy and perinatally, with the majority of studies finding an increased risk of CNS tumors for children whose mothers were exposed to infections during pregnancy [4–6]. The polyomavirus family has been suspected of playing a role in the development of CNS and brain cancers since their DNA has been found in brain tumor tissues, but whether the virus causes these tumors remains unknown [7–9].

Findings on the association of birth weight and childhood CNS tumors are inconsistent. Two studies reported an association between CNS tumors and low birth weight [10,11]. Other investigators found an increased risk of certain subtypes of CNS tumors in children with high birth weight but the associations were dependent on reference group and most of these associations were imprecise. Some studies detected increased risk of astrocytoma for high birth weight (>4000 g) compared with children with birth weight of 2500–3999 g, but no risk for other subtypes [12,13]. A meta-analysis of 8 studies reported slightly increased risk of astrocytoma and medulloblastoma for high birth weight children [14]. Most other studies found no association with birth weight or birth weight-for-gestational age [15,16].

The majority of studies that have examined birth order and risk of childhood brain tumors have found no association [11–13,17,18]. However, two studies have reported a moderate increase in risk of childhood brain tumors among children who were first born, [19] and several studies found an increase associated with being second or higher born [6,20].

Maternal history of miscarriages was found to be protective against childhood CNS tumors in one study [13]. In another study maternal history of one miscarriage was associated with slightly increased risk of malignant CNS tumors [21]. Most other studies did not find any association [5,10,11,18].

A very few studies have found that the risk of brain tumors increases with advanced maternal age [22]; the majority of studies did not observe an association [5,10–13,18,23]. For paternal age, findings are also inconsistent [23,24].

The majority of studies on parental smoking before and during pregnancy found no or limited association with CNS tumors [5,18,25].

Most previous studies on perinatal risk factors for CNS tumors have had limited numbers of cases. Very few studies have looked at such risk factors as newborn abnormalities and maternal complications/conditions during index pregnancy.

In a large case–control study linking data from the California cancer (1988–2008) and birth (1986–2007) registries, we examined the association of childhood CNS tumors with perinatal factors, including birth weight, birth order and history of pregnancy terminations; maternal and paternal age; newborn abnormalities; and complications/conditions during index pregnancy. The large size of the sample allowed for detailed analysis by subtypes of tumors, which was not possible in most previous research.

2. Materials and Methods

The California Cancer Registry (CCR), a statewide population-based cancer registry, was used to obtain information on diagnosis and subtype of all CNS and brain tumor cases diagnosed between 1988 and 2008 in children younger than 16 years who were born in California and resided in California at the time of diagnosis. The CCR is recognized as one of the leading cancer registries in the world with almost complete registration (99%). The cancer registry routinely recorded age, race/ethnicity, sex, and residence at the time of diagnosis as well as information on cancer types and characteristics [26]. Control subjects were randomly selected from the California Birth Registry and matched to cases (1 to 1) on the basis of date of birth (± 6 months) and sex; controls who had been diagnosed with any type of cancer in California by the age of diagnosis of a case were excluded.

Information on birth weight, birth order, maternal and paternal age, maternal history of pregnancy terminations, complications/conditions during index pregnancy, and newborn abnormalities as well as on child's date of birth, gender, maternal and paternal education, and ethnicity were extracted from California birth records.

Birth weight was evaluated as a categorical variable with 500 g and 1000 g increments and reference <2500 g, as a categorical variable with normal birth weight (2500–4000 g) as reference, as a continuous variable with units of 500 and 1000 g, and as a dichotomous variable with cut points at 3500 g and 4000 g. Categories of birth weight for gestational age, small-for-gestational-age (SGA), average-for-gestational-age (AGA), large-for-gestational-age (LGA), were constructed using U.S. national reference for fetal growth by Alexander (1996) [27].

To evaluate dose-response relationships between birth weight and CNS tumors, we obtained odds ratios using a moving window of birth weight with a width of 1000 g. This analysis used overlapping birth weight categories (windows) of 2500 to <3500 g, 3000 to <4000 g, 3500 to <4500 g, 4000–5000 g and 4500 g with reference category <2500 g, and was adjusted for potential confounders.

Gestational age maternal and paternal ages were analyzed as categorical variables. Gestational age was calculated based on last menstrual period and date of birth. Birth order (1st versus other), history of maternal pregnancy terminations, maternal conditions/complications during index pregnancy and newborn abnormalities were analyzed as dichotomous variables (yes or no).

The primary analysis method was conditional logistic regression using the one-to-one age and gender matched case–control pairs [28]. We evaluated the association of CNS tumors and variables of interest both unadjusted and adjusted for potential confounders. Results of these analyses were not materially different; hence we present adjusted results only. For adjusted analyses, covariates were chosen based on information about known or potential

confounders and model fit statistics; models with the lowest Akaike information criterion (AIC) value and lowest number of potential confounders are presented. Father's education and payment source for delivery were used as proxies for socioeconomic status (SES), a potential confounder. For payment source for delivery, governmental programs such as Medicare and MediCal and 'No care' were coded as low SES; private insurance and other sources of payment were coded as middle/high SES. For father's education, 12 years of education was considered low SES, 13–17 years as middle SES, and 17 years as high SES. We confirmed the absence of unduly influential observations by fitting a variety of models with different subsets of covariates and examining the results for outliers and influence.

Despite the large number of cases and controls, sample sizes for some analyses were reduced due to missing data that was attributable largely to differences in the information collected on birth certificates from year to year. No differences in patterns of missingness were detected between cases and controls. Missing data were multiply imputed using Monte Carlo Markov chain full-data imputation under a missing at random assumption [29,30] implemented by the MI procedure in SAS 9.2 [31], and analyses were repeated on the multiply imputed data using the MIANALYZE procedure. The imputation model included all variables used in models (except newborn abnormalities and complications/conditions during index pregnancy) and auxiliary variables likely to be correlated with variables of interest (number of pregnancy visits, month prenatal care began, type of birth, planned place of birth, number of ever born children, number of children born alive, and number of children born alive now deceased).

Analyses were conducted using SAS 9.2 statistical software [31]. The study was approved by University of California, Los Angeles Office for the Protection of Research Subjects and the California Office for the Protection of Human Subjects.

3. Results

A total of 3858 childhood CNS and brain tumor cases that met our inclusion criteria were identified from the California cancer registry. Linkage to birth records was successful for 3308 cases (85.7%), and this constituted the analytic sample. There were 1375 astrocytoma, 434 glioma, 279 ependymoma, 311 primitive neuroectodermal embryogenic tumor (PNET), 394 medulloblastoma and 323 other CNS tumor cases; 192 cases were missing information on type of tumor. Of the 3308 subjects, 1769 were male (53.5%) and 1539 were female (46.5%). The mean age at diagnosis was 5.6 years with a range of 0 to 15.6 years. Table 1 shows other characteristics of study subjects.

Socio-demographic and perinatal characteristics of study subjects by CNS tumor subtype are available as online supplemental material (Table 1a).

In Table 2 we show results of conditional logistic regression analyses for associations of childhood CNS tumors and various perinatal factors.

3.1. Birth Weight

In the analysis of birth weight as a continuous variable, risk increased with increasing weight, with adjusted ORs for total CNS per 500 g and 1000 g increase. In categorical analyses, including the one with normal birth weight as reference, adjusted ORs also exceeded unity for higher birth weight babies, but estimates were imprecise (Table 1).

To address concerns about birth weight misclassification due to chosen cut points and to further examine trend, we obtained odds ratios using a moving window for birth weight categorized as 2500–<3500 g, 3000–<4000 g, 3500–<4500 g, 4000–5000 g, >4500 g with a

reference category <2500 g, with adjustment for potential confounders (Fig. 1). No clear trend was detected for the association of birth weight and childhood CNS tumors. Analyses using weight-for-gestational-age categories similarly yielded elevated point estimates but were also consistent with no increased risk.

3.2. Gestational Age

Analysis of gestational age adjusted for birth weight, birth order, mother's age, father's education, child's race, and payment source for delivery, entered in the model as a dichotomous variable or 3-level categorical variable, did not yield evidence of increased risk associated with more advanced gestational age (Table 2).

3.3. Birth Order

No association was detected between birth order and childhood CNS tumors.

3.4. Parental Age

A small increased risk of CNS tumors was observed for 5-year increase in maternal and paternal ages (Table 2). Similar result was found in the categorical analysis but with wider confidence intervals, with highest risk among mothers who were more than 35 year-old.

3.5. Other Prenatal Factors

Maternal history of pregnancy terminations, either before or after 20 weeks of gestation, was not associated with risk of CNS tumors in children.

Among maternal complications/conditions during index pregnancy, genital herpes and blood and immune disorders were associated with increased risk and non-sexually transmitted infections were associated with decreased risk (Table 2). Among newborn abnormalities, only CNS abnormalities were associated with higher risk of childhood CNS tumors.

Models with interactions between birth weight and birth order, mother's age, child's race, and source of payment for care were also considered. None of the interaction models showed any important findings (results not presented).

3.6. CNS Tumor Subtypes

The large sample size allowed us to perform analyses by CNS tumor subtype, although numbers for some subtypes were small. In Table 3, we present results of adjusted conditional logistic regression analysis for associations of various perinatal factors with subtypes of childhood CNS tumors.

High birth weight was associated with slightly increased risk of astrocytoma and glioma, although confidence intervals were wide. Birth weight-for-gestational age was positively associated with the risk of glioma and negatively associated with the risk of ependimoma. (Table 3)

Advanced maternal age was associated with increased risk of glioma and advanced paternal age was associated with small increase in risk of astrocytoma (Table 3).

There was little evidence of any associations of maternal complications during pregnancy or newborn abnormal conditions with risk of any type of childhood CNS tumors examined. There was a numerically high but imprecisely estimated risk of medulloblastoma associated with maternal blood and immune disorders during pregnancy and numerically low but imprecisely estimated risk of astrocytoma and medulloblastoma with maternal non-sexually transmitted infections (Table 3).

After performing complete case analyses, analyses were repeated using multiply imputed data. Estimates from these two types of analyses were very similar, but more precise for multiply imputed data. No other important differences were observed for the associations of perinatal factors and childhood CNS tumors between complete case and multiply imputed data analysis (results not presented).

4. Discussion

In our analysis we observed a slightly increased risk for total CNS tumors for high birth weight infants but no clear dose response. These findings are in line with other studies that reported a slightly increased risk of CNS tumors for high birth weight babies, but findings have been inconsistent. Meta-analysis by Harder et al. (2008) found slightly increased risk of astrocytoma and medulloblastoma for high birth weight children [14]. Some studies detected increased risk of astrocytomas only [12,13]. In analyses by subtype, we observed numerically higher point estimates of risk for astrocytoma and medulloblastoma as well as for other subtypes.

Some authors have suggested that birth weight alone is not a good predictor for the development of childhood cancers and that birth weight for gestational age as an indicator for fetal growth could be a better predictor for brain tumors. When we examined birth weight for gestational age, the results indicated no increase in risk of total CNS tumors for either LGA or SGA babies compared to AGA. In analyses by subtype, a 1.9-fold increased risk of glioma was observed for LGA babies. Interestingly, for ependymoma, we found a 2.6-fold increased risk for SGA babies. Such results for subtype analysis could be due to chance or to different risk factors for different subtypes.

Like the majority of studies, we did not find any association between birth order and either total CNS tumors or subtypes.

Our results revealed a weak positive association of advanced maternal and paternal ages and CNS tumors: 6% increased risk for 5-year increase in maternal age and 5% for 5-year increase in paternal age. In subtype analysis we observed increased risk of astrocytoma for 5-year increase in paternal age and of glioma for paternal age greater than 35 years old (<25 years old as reference). Although many studies did not find associations with parental age [12,19,32,33], some studies showed results similar to ours. Hemminki et al. [23] found an increased risk of CNS tumors and advanced paternal age; Macmahon et al. (1962) found an increased risk with advanced maternal age [22]. Reproductive parental age may affect the risk of childhood cancers in several ways. Frequencies of paternal and maternal germ cell mutations increase with age and thus may increase the chance of developing cancer in a child [34]. Other mechanisms could include differential expression of genes in cell cycle control and changes in DNA damage response and repair pathways in oocytes of older mothers [35]. Aging may also change physiological parameters, such as estrogens levels, which may also increase risk of cancer [34]. Older age, particularly of the mother, appears to be a risk factor across many of the common childhood cancer types [35].

There were several maternal complications or conditions during pregnancy that we found potentially associated with CNS tumors and some subtypes. Genital herpes and blood and immunological disorders during index pregnancy were associated with marked increased risk of total CNS tumors (OR = 2.74 and OR = 2.28, respectively). Increase in risk associated with blood and immune disorders was probably due to a large (about 7-fold) but imprecise increase in risk of medulloblastoma. Several other studies found an increased risk of CNS tumors in children whose mothers had viral infections during pregnancy [4], but there were no studies that investigated genital herpes infection specifically. Viral material has been found in almost all types of CNS tumors [7,9]. Although the presence of viral

substance does not prove a causal relationship with tumor formation, it does suggest the hypothesis that viruses maybe involved [7–9,36]. Interestingly, we observed a decreased risk of CNS tumors in children whose mothers had other non-sexually transmitted infections during pregnancy. It was not possible to identify type of infection during pregnancy; thus our results could be due to bacterial or various combinations of infections.

Newborn CNS abnormalities were associated with 4-fold increased risk of CNS tumors. Other newborn abnormalities such as Down's syndrome, musculoskeletal, digestive system, face and neck abnormalities were not associated with the risk of CNS tumors. We did not find any other studies that looked at the association of CNS/brain tumors and newborn abnormalities except that of Partap et al. (2011), which found an increased risk associated with newborn birth defects (non-specific) [37].

We did not find any association between CNS tumors or their subtypes and other perinatal factors such as gestational age, history of pregnancy terminations, eclampsia or preeclampsia, anemia, chronic conditions, and maternal tobacco smoking. We did not find studies that looked at similar factors in association with CNS tumors, except studies on maternal tobacco smoking that also found no association [5,18,25].

Our study had strengths and limitations. A major strength was that our data were from population registries with almost complete registration of births and cancers in California and controls were randomly selected from the birth registry rather than recruiting volunteers as in many case–control studies. Since these registries are independent of each other and participation of subjects was not required for our data collection, selection and information biases are unlikely in this study. This is not the case for studies based on questionnaires and interviews, which are subject to serious participation and recall bias issues. Misclassification of outcome status was also unlikely in this study due to the completeness and high accuracy of the California Cancer Registry. Misclassification of birth weight was possible but unlikely since birth weight is usually recorded very accurately [38]. There are very few validation studies on quality of reporting for some variables on California birth certificates. Validation studies on accuracy of reporting of health insurance and birth weight has shown high concordance between recorded and interview data, but for other variables, such as gestational age, accuracy was lower, especially after 1992 [38,39]. Based on aforementioned information we assumed that it is possible that some perinatal factors, particularly complications during pregnancy and newborn abnormalities, are subject to some misreporting. Information was not routinely collected for many maternal and newborn conditions prior to 1990 and in addition, the very small numbers of such subjects leads us to suspect underreporting. Uncertain accuracy of reporting together with underreporting could have led to misclassification in those variables, which most likely would have biased results towards the null.

Another advantage of this study was that the large size of the dataset allowed us to carry out analyses for subtypes of CNS tumors.

We adjusted for potential confounders that were available in registries such as ethnicity, parental education, and sources of payment for delivery as proxies for socioeconomic status. Adjustment for the majority of these variables did not make a difference in estimates of risk for birth weight and other perinatal factors. There was little or no information available on such potential confounders as maternal and paternal occupation, diet, alcohol and drug use, maternal health conditions before pregnancy and child's abnormal conditions. Therefore, residual confounding was possible. It was unlikely that maternal occupation and alcohol and drug use could considerably bias the association of birth weight and brain tumors since these factors are inversely associated with birth weight [40–42] but positively associated with

childhood CNS tumors [13,24,43–47]. Therefore, even if we considered bias due to these variables possible, it would most likely pull the estimate toward the null.

A limitation of the study was missing data. However, since information was missing mainly due to differences in the information collected on birth certificates from year to year rather than non-response, the potential for biases was probably small, and the impact was mainly on the precision of the estimates. For example, information on parental education and several maternal and newborn conditions was available only for more recent years. There was no difference in the pattern of missingness between cases and controls. We reanalyzed the data using multiple imputation and obtained similar results.

In summary, we found that maternal genital herpes, blood and immunological disorders during pregnancy and newborn CNS abnormalities were associated with increased risk of CNS tumors. Maternal infections during pregnancy were associated with decreased risk. Advanced maternal and paternal ages were also associated with slightly increased risk of CNS tumors. Factors associated with subtypes of CNS tumors varied by subtype, which could be expected due to different etiology for different subtypes.

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References

1. Gurney, G.; Smith, MA.; Bunin, GR. CNS and miscellaneous intracranial and intraspinal neoplasms in SEER pediatric monograph. Bethesda: N.C. Institute, SEER; 1999. p. 51-64.
2. National Cancer Institute. A snapshot of brain and central nervous system cancers. Bethesda, MD: National Cancer Institute, Office of Science Planning and Assessment; 2008.
3. Gurney, G.; Smith, MA.; Bunin, GR. CNS and miscellaneous intracranial and intraspinal neoplasms in SEER pediatric monograph. Bethesda: N.C. Institute, SEER; 2001. p. 51-64.
4. Dickinson HO, Nyari TA, Parker L. Childhood solid tumours in relation to infections in the community in Cumbria during pregnancy and around the time of birth. *Br J Cancer*. 2002; 87(7): 746–50. [PubMed: 12232758]
5. Fear NT, Roman E, Ansell P, Bull D. Malignant neoplasms of the brain during childhood: the role of prenatal and neonatal factors (United Kingdom). *Cancer Causes Control*. 2001; 12(5):443–9. [PubMed: 11545459]
6. Shaw AK, Li P, Infante-Rivard C. Early infection and risk of childhood brain tumors (Canada). *Cancer Causes Control*. 2006; 17(10):1267–74. [PubMed: 17111258]
7. Baldwin RT, Preston-Martin S. Epidemiology of brain tumors in childhood – a review. *Toxicol Appl Pharmacol*. 2004; 199(2):118–31. [PubMed: 15313584]
8. Vilchez RA, Butel JS. SV40 in human brain cancers and non-Hodgkin's lymphoma. *Oncogene*. 2003; 22(33):5164–72. [PubMed: 12910253]
9. Khalili K, Del Valle L, Otte J, Weaver M, Gordon J. Human neurotropic polyomavirus, JCV, and its role in carcinogenesis. *Oncogene*. 2003; 22(33):5181–91. [PubMed: 12910255]
10. Schuz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med Pediatr Oncol*. 2001; 36(2):274–82. [PubMed: 11452935]
11. McCredieM, Little J, Cotton S, Mueller B, Peris-Bonet R, Choi NW, et al. SEARCH international case-control study of childhood brain tumours: role of index pregnancy and birth, and mother's reproductive history. *Paediatr Perinat Epidemiol*. 1999; 13(3):325–41. [PubMed: 10440052]

12. Von Behren J, Reynolds P. Birth characteristics and brain cancers in young children. *Int J Epidemiol.* 2003; 32(2):248–56. [PubMed: 12714545]
13. Kuijten RR, Bunin GR, Nass CC, Meadows AT. Gestational and familial risk factors for childhood astrocytoma: results of a case–control study. *Cancer Res.* 1990; 50(9):2608–12. [PubMed: 2328486]
14. Harder T, Plagemann A, Harder A. Birth weight and subsequent risk of childhood primary brain tumors: a meta-analysis. *Am J Epidemiol.* 2008; 168(4):366–73. [PubMed: 18579539]
15. Sprehe MR, Barahmani N, Cao Y, Wang T, Forman MR, Bondy M, et al. Comparison of birth weight corrected for gestational age and birth weight alone in prediction of development of childhood leukemia and central nervous system tumors. *Pediatr Blood Cancer.* 2010; 54(2):242–9. [PubMed: 19813253]
16. Smith A, Lightfoot T, Simpson J, Roman E, UKCCS investigators. Birth weight, sex and childhood cancer: a report from the United Kingdom childhood cancer study. *Cancer Epidemiol.* 2009; 33(5):363–7. [PubMed: 19932649]
17. Heuch JM, Heuch I, Akslen LA, Kvale G. Risk of primary childhood brain tumors related to birth characteristics: a Norwegian prospective study. *Int J Cancer.* 1998; 77(4):498–503. [PubMed: 9679748]
18. Linet MS, Gridley G, Cnattingius S, Nicholson HS, Martinsson U, Glimelius B, et al. Maternal and perinatal risk factors for childhood brain tumors (Sweden). *Cancer Causes Control.* 1996; 7(4):437–48. [PubMed: 8813432]
19. Emerson JC, Malone KE, Daling JR, Starzyk P. Childhood brain tumor risk in relation to birth characteristics. *J Clin Epidemiol.* 1991; 44(11):1159–66. [PubMed: 1941011]
20. Pavlovic MV, Jarebinski MS, Pekmezovic TD, Janicijevic MA. Risk factors from brain tumors in children and adolescents: a case–control study in Belgrade, Serbia. *Eur J Neurol.* 2005; 12(7):508–13. [PubMed: 15958089]
21. Mallol-Mesnard N, Menegaux F, Lacour B, Hartmann O, Frappaz D, Doz F, et al. Birth characteristics and childhood malignant central nervous system tumors: the ESCALE study (French Society for Childhood Cancer). *Cancer Detect Prev.* 2008; 32(1):79–86. [PubMed: 18396378]
22. Macmahon B, Newill VA. Birth characteristics of children dying of malignant neoplasms. *J Natl Cancer Inst.* 1962; 28:231–44. [PubMed: 14468028]
23. Hemminki K, Kyyronen P, Vaittinen P. Parental age as a risk factor of childhood leukemia and brain cancer in offspring. *Epidemiology.* 1999; 10(3):271–5. [PubMed: 10230837]
24. Cordier S, Monfort C, Filippini G, Preston-Martin S, Lubin F, Mueller BA, et al. Parental exposure to polycyclic aromatic hydrocarbons and the risk of childhood brain tumors: the SEARCH international childhood brain tumor study. *Am J Epidemiol.* 2004; 159(12):1109–16. [PubMed: 15191928]
25. Norman MA, Holly EA, Ahn DK, Preston-Martin S, Mueller BA, Bracci PM. Prenatal exposure to tobacco smoke and childhood brain tumors: results from the United States West Coast childhood brain tumor study. *Cancer Epidemiol Biomarkers Prev.* 1996; 5(2):127–33. [PubMed: 8850274]
26. The California Cancer Registry. Mission Statement & Purpose. Mar. 2009 Available from: <http://www.ccrca.org/abouttheccr.html>
27. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol.* 1996; 87(2):163–8. [PubMed: 8559516]
28. Hosmer, DW., Jr; Lemeshow, S. *Applied logistic regression.* New York: Wiley; 2000.
29. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Medicine.* 1991; 10(4):585–98.
30. Little, R.; Rubin, D. *Statistical analysis with missing data.* 2nd. New York: Wiley; 2002.
31. SAS Institute Inc. *SAS statistical software.* NC: Cary; 2006.
32. Samuelson SO, Bakketeig LS, Tretli S, Johannesen TB, Magnus P. Head circumference at birth and risk of brain cancer in childhood: a population-based study. *Lancet Oncol.* 2006; 7(1):39–42. [PubMed: 16389182]
33. McKinney PA, Juszczak E, Findlay E, Smith K, Thomson CS. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: a Scottish case control study. *Br J Cancer.* 1999; 80(11):1844–51. [PubMed: 10468308]

34. Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. *Int J Epidemiol.* 2006; 35(6):1495–503. [PubMed: 17008361]
35. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Parental age and risk of childhood cancer: a pooled analysis. *Epidemiology.* 2009; 20(4):475–83. [PubMed: 19373093]
36. Bondy M, Ligon BL. Epidemiology and etiology of intracranial meningiomas: a review. *J Neuro-Oncol.* 1996; 29(3):197–205.
37. Partap S, Maclean J, Von Behren J, Reynolds P, Fisher PG. Birth anomalies and obstetric history as risks for childhood tumors of the central nervous system. *Pediatrics.* 2011; 128(3):e652–7. [PubMed: 21824884]
38. Remy, L.; Oliva, G. Impact of data quality on birth related health indicators Family health outcomes project, report. San Francisco: University of California San Francisco; 2006.
39. Braveman P, Pearl M, Egerter S, Marchi K, Williams R. Validity of insurance information on California birth certificates. *Am J Public Health.* 1998; 88(5):813–6. [PubMed: 9585754]
40. Bada HS, Das A, Bauer CR, Shankaran S, Lester BM, Gard CC, et al. Low birth weight and preterm births: etiologic fraction attributable to prenatal drug exposure. *J Perinat.* 2005; 25(10):631–7.
41. Day NL, Jasperse D, Richardson G, Robles N, Sambamoorthi U, Taylor P, et al. Prenatal exposure to alcohol: effect on infant growth and morphologic characteristics. *Pediatrics.* 1989; 84(3):536–41. [PubMed: 2771556]
42. Richardson GA, Hamel SC, Goldschmidt L, Day NL. Growth of infants prenatally exposed to cocaine/crack: comparison of a prenatal care and a no prenatal care sample. *Pediatrics.* 1999; 104(2):pe18.
43. Cordier S, Iglesias MJ, Le Goaster C, Guyot MM, Mandereau L, Hemon D. Incidence and risk factors for childhood brain tumors in the Ile de France. *Int J Cancer.* 1994; 59(6):776–82. [PubMed: 7989118]
44. Cordier S, Mandereau L, Preston-Martin S, Little J, Lubin F, Mueller B, et al. Parental occupations and childhood brain tumors: results of an international case–control study. *Cancer Causes Control.* 2001; 12(9):865–74. [PubMed: 11714115]
45. McKean-Cowdin R, Preston-Martin S, Pogoda JM, Holly EA, Mueller BA, Davis RL. Parental occupation and childhood brain tumors: astroglial and primitive neuroectodermal tumors. *J Occup Environ Med.* 1998; 40(4):332–40. [PubMed: 9571524]
46. Milne E, Greenop KR, Scott RJ, De Klerk NH, Bower C, Ashton LJ, et al. Parental alcohol consumption and risk of childhood acute lymphoblastic leukemia and brain tumors. *Cancer Causes Control.* 2013; 24(2):391–402. [PubMed: 23247637]
47. Preston-Martin S, Yu MC, Benton B, Henderson BE. N-Nitroso compounds and childhood brain tumors: a case–control study. *Cancer Res.* 1982; 42(12):5240–5. [PubMed: 7139628]

Fig. 1. Conditional odds ratios (OR) and 95% confidence intervals (CI) for childhood CNS tumors at moving windows of birth weight, matched on child's age and sex and adjusted for child's race, gestational age, mother's age, birth order, father's education and source of payment for delivery. Reference level: <2500 g.

Socio-demographic and perinatal characteristics of childhood brain and central nervous system tumor cases and controls, California birth registry, 1986–2007.

Table 1

Variables	Total N	Cases N (%)	Controls N (%)
Child's age at diagnosis	6616	3308	3308
<1 year	670	335 (10.1)	335 (10.1)
1–5 years	3231	1609 (48.6)	1622 (49.0)
6–9 years	1528	768 (23.2)	760 (23.0)
10–15 years	1187	596 (18.0)	591 (17.9)
Mother's age at birth			
<25 years	2261	1054 (31.9)	1207 (36.5)
25–35 years	3359	1711 (51.7)	1648 (49.8)
35 years	995	543 (16.4)	452 (13.7)
Missing	1	0	1
Father's age at birth			
<25 years	1369	635 (20.4)	734 (23.6)
25–35 years	3251	1647 (52.9)	1604 (51.7)
35 years	1598	831 (26.7)	767 (24.7)
Missing	398	195	203
Child's race			
White	5000	2564 (81.0)	2436 (77.8)
Black	555	257 (8.2)	298 (9.5)
Asian	640	295 (9.3)	345 (11.0)
Other	101	48 (1.5)	53 (1.7)
Missing	320	144	176
Hispanic origin of child			
Non-Hispanic	3452	1846 (57.1)	1586 (49.2)
Hispanic	3021	1385 (42.9)	1636 (50.8)
Missing	163	77	86
Father's education			
<12 years	3521	1720 (75.0)	1801 (79.8)
13–17 years	739	416 (18.1)	323 (14.3)
17 years	291	157 (6.9)	134 (5.9)
Missing/not collected ^d	2065	1015	1050
Source of payment for delivery			
Governmental programs	2422	1075 (38.1)	1347 (47.8)
Other insurance	3220	1748 (61.9)	1472 (52.2)

Variables	Total N	Cases N (%)	Controls N (%)
Missing/not collected ^a	974	485	489
Birth weight			
<2500g	408	192 (5.8)	216 (6.5)
2500–3500g	3406	1655 (50.0)	1751 (52.9)
3500–4500g	2679	1399 (42.3)	1280 (38.7)
4500g	123	62 (1.9)	61 (1.8)
Gestational age at birth			
<37 weeks	645	319 (10.3)	326 (10.5)
37–42 weeks	5005	2499 (80.8)	2506 (80.8)
>42 weeks	542	274 (8.9)	268 (8.7)
Missing/implausible values	424	216	208
Birth order			
First	2606	1331 (40.3)	1275 (38.6)
Other	4003	1973 (59.7)	2030 (61.4)
Missing	7	4	3
Maternal history of terminations before 20 weeks			
No	5508	2741 (82.9)	2767 (83.8)
Yes	1102	564 (17.1)	538 (16.3)
Missing	6	3	3
Maternal history of terminations after 20 weeks			
No	6512	3252 (98.5)	3260 (98.6)
Yes	96	51 (1.5)	45 (1.4)
Missing	8	5	3
Complications/conditions during index pregnancy^b			
None	3173	1561 (47.4)	1612 (48.9)
Preeclampsia/eclampsia	93	45 (1.4)	48 (1.5)
Anemia	38	19 (0.6)	19 (0.6)
Genital herpes	75	50 (1.5)	25 (0.8)
Infections (non-sexually transmitted) ^c	33	11 (0.3)	22 (0.7)
Chronic diseases ^c	145	84 (2.6)	61 (1.8)
Blood and immune disorder ^c	51	32 (1.0)	19 (0.6)
Tobacco use	122	62 (1.9)	60 (1.8)
Newborn abnormalities^b			
CNS	18	15 (0.5)	3 (0.1)
Eye, ear, neck, face	9	3 (0.1)	6 (0.2)
Musculoskeletal	11	7 (0.2)	4 (0.1)

Variables	Total N	Cases N (%)	Controls N (%)
Down's syndrome	12	8 (0.2)	4 (0.1)

^aPatterns of missingness varied by year due to differences in data collection for different years.

^bInformation was not routinely collected for many of these conditions for years prior to 1990; therefore there is substantial amount of missing data for these conditions.

^cInfections during pregnancy include pyelonephritis, hepatitis B and rubella. Chronic diseases include renal, cardiac, lung diseases, hypertension and diabetes. Blood and immune disorders include Rh sensitization, hemaglobinopathy, uterine bleeding before labor.

Table 1a

Socio-demographic and perinatal characteristics of study subjects by subtype, California birth registry, 1986–2007.

Variables	Total #	Astrocytoma Cases/controls	Glioma Cases/controls	Ependi-moma Cases/controls	PNET Cases/controls	Medullo-blastoma Cases/controls	Other Cases/controls
Child's age							
<1 year	670	108/107	26/22	27/28	38/43	30/31	60/55
1–5 years	3231	678/683	189/196	150/154	200/194	197/200	142/145
6–9 years	1528	321/320	135/129	59/53	50/52	114/112	46/50
10–15 years	1187	264/261	84/87	43/44	23/22	51/49	68/66
Mother's age							
<25 years	2261	414/502	127/150	92/95	120/114	142/152	94/126
25–35 years	3359	756/682	219/228	142/133	146/157	200/198	158/150
35–45 years	995	205/191	88/56	45/51	45/40	52/43	71/47
Missing	1	0/0	0/0	0/0	0/0	0/1	0/0
Father's age							
<25 years	1369	261/311	86/99	51/51	75/80	83/82	44/68
25–35 years	3251	693/686	195/198	133/143	162/139	191/198	168/143
35–45 years	1598	355/306	122/109	72/64	55/78	91/80	95/91
Missing	398	66/72	31/28	23/21	19/14	29/34	16/21
Child's race							
White	5000	1086/997	335/332	213/209	243/243	326/282	233/235
Black	555	108/137	39/30	22/27	29/28	18/35	21/23
Asian	640	115/158	39/42	26/25	24/29	28/43	33/25
Other	101	20/26	3/10	2/3	4/2	2/5	9/4
Missing	320	46/57	18/20	16/15	11/9	20/29	27/36
Hispanic origin of child							
Non-hispanic	3432	836/691	243/210	138/126	160/147	196/180	168/138
Hispanic	3021	515/652	183/215	129/148	147/160	186/199	143/171
Missing	163	24/32	8/9	12/5	4/4	12/15	12/14
Father's education							
12 years	3521	685/720	210/207	154/167	157/172	206/220	197/203
13–17 years	739	173/132	34/45	37/22	31/23	63/42	57/37
17 years	291	64/50	20/19	13/16	12/10	17/14	20/17

Variables	Total #	Astrocytoma Cases/controls	Glioma Cases/controls	Ependi-moma Cases/controls	PNET Cases/controls	Medullo-blastoma Cases/controls	Other Cases/controls
Missing/not collected ^a	2065	453/473	170/163	75/74	111/106	108/118	49/66
Source of payment for delivery							
Governmental programs	2422	404/565	151/158	95/109	110/117	138/173	103/145
Other insurance	3220	741/573	201/194	155/140	139/132	209/179	205/162
Missing/not collected ^a	974	230/237	82/82	29/30	62/62	47/42	15/16
Birth weight							
<2500g	408	64/78	25/41	12/21	28/21	26/25	24/21
2500–3500g	3406	679/724	217/213	162/140	149/165	189/215	160/183
3500–4500g	2679	606/542	188/171	102/116	126/121	169/145	135/115
4500g	123	26/31	4/9	3/2	8/4	10/9	4/4
Gestational age							
<37 weeks	645	111/132	43/41	23/30	37/29	44/39	39/38
37–42 weeks	5005	1067/1045	329/329	215/204	224/235	290/299	238/244
>42 weeks	542	109/112	41/34	22/24	28/26	34/31	24/25
Missing/implausible values	424	88/86	21/30	19/21	22/21	26/25	22/16
Birth order							
First	2606	564/531	146/168	112/97	128/125	178/148	121/132
Other	4003	811/844	288/265	166/182	182/186	216/245	201/191
Missing	7	0/0	0/1	1/0	1/0	0/1	1/0
Maternal history of terminations before 20 weeks							
No	5508	1148/1160	357/374	221/232	261/250	391/319	260/274
Yes	1102	227/215	77/59	58/47	49/61	3/73	62/49
Missing	6	0/0	0/1	0/0	1/0	0/2	1/0
Maternal history of terminations after 20 weeks							
No	6512	1354/1357	424/426	274/276	304/305	334/384	316/320
Yes	96	20/18	10/7	4/3	6/6	60/8	6/3
Missing	8	1/0	0/1	1/0	1/0	0/2	1/0
Complications/conditions during index pregnancy^b							
None	3173	671/685	226/216	122/145	161/154	186/193	111/133
Preeclampsia/eclampsia	93	16/28	7/5	0/1	5/5	3/4	10/1
Anemia	38	10/6	0/2	0/1	3/1	3/4	1/3

Variables	Total #	Astrocytoma Cases/controls	Glioma Cases/controls	Ependi-moma Cases/controls	PNET Cases/controls	Medullo-blastoma Cases/controls	Other Cases/controls
Genital herpes	75	20/14	8/1	2/0	4/3	9/5	3/1
Infections (non-sexually transmitted) ^c	33	6/11	1/2	1/3	1/1	1/3	0/1
Chronic diseases ^c	145	35/23	13/9	7/4	7/5	9/9	10/5
Blood and immune disorders ^c	51	10/14	5/2	1/1	2/0	8/1	5/0
Tobacco use	122	28/23	10/7	3/5	7/7	8/11	6/6
Newborn abnormalities^b							
CNS	18	2/1	0/1	0/0	3/0	2/0	3/1
Eye, ear, neck, face	9	0/4	0/0	0/0	1/0	1/2	0
Musculoskeletal	11	1/3	0/0	0/0	3/0	2/0	0/1
Down's syndrome	12	0/2	0/0	0/0	2/1	1/1	3/0

^a Patterns of missingness varied by year due to differences in data collection for different years.

^b Information was not routinely collected for many of these conditions for years prior to 1990; therefore there is substantial amount of missing data for these conditions.

^c Infections during pregnancy include pyelonephritis, hepatitis B and rubella. Chronic diseases include renal, cardiac, lung diseases, hypertension and diabetes. Blood and immune disorders include Rh sensitization, hemagglutininopathy, uterine bleeding before labor.

Table 2

Adjusted conditional odds ratios (OR) and 95% confidence intervals for childhood CNS tumors and various risk factors, matched on age and sex. California birth registry, 1986–2007.

Variables	Adjusted OR	Lower 95% confidence interval	Upper 95% confidence interval
Birth weight^a			
Continuous, per 500g increase	1.06	0.99	1.12
Continuous, per 1000g increase	1.11	0.99	1.24
<2500g	1	–	–
2500–3500g	1.19	0.89	1.60
3500–4500g	1.24	0.91	1.69
4500g	1.24	0.70	2.19
<3500g	1	–	–
3500g	1.06	0.92	1.22
<4000g	1	–	–
4000g	1.12	0.91	1.39
<2500g	0.84	0.63	1.12
2500–4000g	1	–	–
>4000g	1.12	0.91	1.38
SGA	0.96	0.75	1.23
AGA	1	–	–
LGA	1.09	0.89	1.27
Gestational age^b			
<37 weeks	1	–	–
37–42 weeks	0.96	0.74	1.23
42 weeks	1.08	0.76	1.52
Birth order^c			
First	1	–	–
Other	0.92	0.79	1.06
Mother's age^d			
by 5-year increase	1.06	1.00	1.12
<25 years	1	–	–
25–35 years vs <25 years	1.12	0.96	1.30
>35 years vs <25 years	1.21	0.98	1.49
Father's age^d			
by 5-year increase	1.05	1.00	1.10
<25 years	1	–	–
25–35 years vs <25 years	1.18	0.99	1.41
35 years vs < 25 years	1.16	0.94	1.43
Maternal history of terminations before 20 weeks^e			
No	1	–	–
Yes	1.13	0.94	1.35

Variables	Adjusted OR	Lower 95% confidence interval	Upper 95% confidence interval
Maternal history of termination s after 20 weeks^e			
No	1	—	—
Yes	1.28	0.71	2.32
Complications/conditions during index pregnancy^e			
Preeclampsia/eclampsia	0.78	0.42	1.41
Anemia	1.04	0.48	2.29
Genital herpes	2.79	1.17	6.62
Infections (non-sexually transmitted)	0.28	0.09	0.85
Chronic diseases	1.31	0.84	2.03
Blood and immune disorders	2.32	1.09	4.91
Tobacco use	1.86	0.73	1.91
Newborn abnormalities^e			
CNS	4.30	1.19	15.53
Eye, ear, neck, face	0.42	0.08	2.30
Musculoskeletal	1.12	0.30	4.24
Down's syndrome	2.06	0.50	8.47

^a Adjusted for child's race, gestational age, birth order, mother's age, father's education and source of payment for delivery.

^b Adjusted for child's race, birth weight, birth order, mother's age, father's education, source of payment for delivery.

^c Adjusted for child's race, gestational age, father's education, mother's age, source of payment for delivery.

^d Adjusted for child's race, birth order, father's education, and source of payment for delivery.

^e Adjusted for child's race, birth weight, gestational age, birth order, mother's age, father's education and source of payment for delivery.

Table 3

Adjusted conditional odds ratios (OR) and 95% confidence intervals (CI) for childhood CNS tumors by subtype and several perinatal factors, matched on child's age and sex. California birth registry, 1986–2007.

	Astrocytoma		Glioma		Ependymoma		PNET		Medulloblastoma						
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI					
Birth weight^d															
By 500g increase	1.07	0.97	1.19	1.10	0.92	1.32	0.95	0.77	1.17	1.11	0.91	1.36	1.12	0.92	1.35
By 1000g increase	1.17	0.97	1.42	1.23	0.88	1.72	0.94	0.65	1.37	1.23	0.83	1.82	1.28	0.90	1.83
<2500g	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
2500–3500g	1.12	0.68	1.83	1.93	0.86	4.35	1.58	0.47	5.30	0.98	0.38	2.54	0.83	0.30	2.34
3500–4500g	1.26	0.75	2.11	1.54	0.865	3.68	0.91	0.26	3.22	1.11	0.41	2.98	1.12	0.39	3.21
4500g	0.99	0.40	2.48	1.94	0.30	12.71	n/e*	n/e	n/e	1.82	0.35	9.48	0.52	0.10	2.74
3500g vs <3500g	1.11	0.88	1.40	0.85	0.53	1.37	0.66	0.39	1.10	1.20	0.74	1.95	1.26	0.81	1.96
4000 g vs <4000 g	1.09	0.79	1.51	1.80	0.93	3.48	1.58	0.75	3.31	1.01	0.44	2.35	1.06	0.58	1.93
<2500g	0.87	0.53	1.41	0.55	0.25	1.23	0.78	0.24	2.57	0.96	0.37	2.45	1.08	0.39	2.95
2500–4000g	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
4000 g	1.09	0.79	1.50	1.80	0.93	3.50	1.55	0.74	3.27	1.01	0.44	2.35	1.06	0.58	1.94
SGA	0.75	0.50	1.13	0.95	0.44	2.06	2.64	1.10	6.30	0.63	0.29	1.39	1.91	0.73	5.03
AGA	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
LGA	0.96	0.70	1.33	1.86	0.99	3.48	1.41	0.66	3.04	0.93	0.45	1.91	1.22	0.68	2.19
Maternal age^b															
Mother's age (by 5-year increase)	1.07	0.98	1.17	1.12	0.95	1.33	1.06	0.88	1.28	0.89	0.73	1.09	1.13	0.94	1.36
<25 years	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
25–35 years vs <25 years	1.21	0.95	1.54	1.16	0.72	1.87	1.15	0.71	1.87	0.80	0.49	1.31	1.14	0.71	1.83
35 years vs <25 years	1.09	0.79	1.52	1.87	1.00	3.52	0.92	0.45	1.87	0.86	0.40	1.84	1.60	0.79	3.21
Paternal age^b															
Father's age (by 5-year increase)	1.08	1.00	1.16	1.10	0.97	1.26	1.11	0.95	1.31	0.89	0.76	1.04	1.08	0.93	1.25
<25 years	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
25–35 years vs <25 years	1.24	0.94	1.64	1.45	0.83	2.53	1.06	0.57	1.99	1.11	0.63	1.94	0.89	0.53	1.50
35 years vs <25 years	1.33	0.96	1.84	1.63	0.88	3.02	1.54	0.71	3.34	0.49	0.24	1.03	0.99	0.51	1.93

	Astrocytoma		Glioma		Ependymoma		PNET		Medulloblastoma	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Maternal complications/conditions during index pregnancy^c										
Eclampsia	0.55	0.21	1.40	0.82	0.11	6.27	n/e	n/e	n/e	0.95
Anemia	2.09	0.52	8.41	n/e	n/e	n/e	n/e	n/e	41.67	0.10
Genital herpes	2.25	0.44	11.43	3.41	0.37	31.79	n/e	n/e	13.18	0.26
Infections (non-sexually transmitted)	0.38	0.07	2.01	n/e	n/e	n/e	n/e	n/e	–	0.05
Chronic conditions	1.94	0.91	4.12	1.70	0.45	6.46	3.08	0.32	29.39	0.98
Blood disorders	1.14	0.37	3.51	1.73	0.24	12.69	–	–	n/e	n/e
Tobacco use	1.79	0.79	4.02	2.10	0.49	9.02	n/e	n/e	3.79	0.84
Newborn abnormalities^c										
CNS	0.72	0.04	13.15	n/e	n/e	n/e	–	–	n/e	n/e
Eye, ear, neck, face	n/e	n/e	n/e	–	–	–	–	–	n/e	n/e
Musculoskeletal	0.25	0.02	2.73	–	–	–	–	–	n/e	n/e
Down's syndrome	n/e	n/e	n/e	–	–	–	–	–	22.37	n/e

* n/e – not estimable

^a Adjusted for child's race, gestational age, birth order, mother's age, father's education and source of payment for delivery

^b Adjusted for child's race, birth order, father's education, and source of payment for delivery

^c Adjusted for child's race, birth weight, gestational age, birth order, mother's age, father's education, source of payment for delivery.