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The risk of childhood brain tumors associated with delivery interventions: A Danish matched case-control study

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Abstract

Background: Head trauma has been associated with increased brain tumor risk in adults. Instrument assisted delivery can be a cause of head trauma in newborns. The goal of this study was to determine if instrument-assisted deliveries influenced the odds of childhood brain tumors in Denmark.

Methods: We conducted a matched case-control study of childhood (<20 years) brain tumors in Denmark born between 1978 and 2013 and diagnosed 1978—2016. A total of 1678 brain tumor cases were identified and 25 controls were matched to each case based on the child's sex and birth date (N = 40,934). Conditional logistic regression was used to estimate effects (odds ratios (OR) and 95% confidence intervals (95%CI)) for variables of interest.

Results: Compared to children birthed by spontaneous vaginal delivery, children who later developed ependymomas (N = 118) had a greater likelihood of having experienced vacuum assisted deliveries (OR=1.74, 95% CI 1.02—2.96). We did not observe an overall increase in all CNS tumors (combined) with either vacuum delivery (OR=0.99, 95% CI 0.84—1.18) or forceps delivery (OR=1.26, 95% CI 0.78—2.03).

Conclusion: Our findings suggest an association between vacuum assisted deliveries and ependymomas.

Keywords: Brain neoplasms; Pediatric cancer epidemiology; Delivery complications; Instrument-assisted delivery; Cesarean section

Introduction

Brain and central nervous system tumors (CNS) make up approximately 20% of the total cancer burden in children worldwide [1, 2]. In Denmark, the CNS tumor rate in children <15 years old is 3.95 per 100,000 children [3]. There are over 100 subtypes of childhood brain tumors and their rarity makes these diseases challenging to study [3]. The most common brain tumor types arise from glial cells, of which astrocytoma and medulloblastoma are the most common types [1, 4, 5]. According to the International Agency for Research on Cancer, the only established carcinogen for brain tumors is ionizing radiation [6], while suspected carcinogens include infections and allergens [3]. The onset of many childhood brain tumors before the age of five indicates potentially relevant exposures occur during early life [1, 3, 7].

Severe head injuries may be a cause of adult brain tumors [8-11], particularly meningioma and glioma [11-14]. There is a possibility that childhood or perinatal head trauma could also lead to tumor formation [15]. Some studies have indicated that there may be an association between instrument-assisted delivery and childhood brain tumors [2, 16-20], including a recent study which found an increased risk of CNS tumors with instrument assisted deliveries (OR=7.82, 95% CI 2.18—28.03) [19].

Vacuum and forceps assisted deliveries are commonly used during vaginal births. In the 2015 European Perinatal Health report, Denmark reported that 6.4% of deliveries were instrument assisted while 21.6% of

births occurred by cesarean section [21]. Large babies (>4000 g) more frequently require instrument assisted delivery, particularly if their mothers are short in stature [22, 23]. These labor procedures can sometimes lead to head trauma, including intracranial hemorrhages (0.15% of forceps assisted births and 0.12% of vacuum assisted births), facial nerve injury, and seizures [24, 25].

Recently, a growing field of research has examined whether delivery by cesarean section might increase risk for pediatric cancer, with many studies focusing on acute leukemias [26, 27]. Possible biological mechanisms may stem from microbiome differences or different breastfeeding habits due to cesarean sections and related antibiotics usage [26]. In addition, children born via cesarean have a greater likelihood of immune disorders later in life [28, 29], including conditions associated with lower risk for brain tumors such as allergies and diabetes [30, 31]. These relationships may be mediated through increased IL-13 and enhanced T-helper (Th2) hyperallergic immunity. Allergy is correlated with Th1 and Th2, both which may help inhibit tumors. Gliomas express high amounts of cytokines that inhibit Th1 and Th2 immunity and are secreted by T-regulatory (Treg) cells [32]. There are few studies on the relationship between cesarean section and childhood CNS tumors [2, 20, 33-35].

Following published results that head trauma of assisted delivery could lead to potential brain tumors in childhood, this study aims to examine if the use of instrument-assisted delivery techniques increased the risk of

childhood brain tumors in the Danish childhood (0—19 years) population. In exploratory analyses, we additionally examined associations between brain tumors and delivery by cesarean section. An earlier study already examined cesarean section in the Denmark population from 1973 to 2007; the current study includes additional years of data [36].

Methods

This is a matched case-control study based on linkage of multiple Danish registries, which has been previously described [37]. In brief, cases were ascertained from the Danish Cancer Registry and classified according to the International Classification of Childhood Cancers (ICCC) based on the existing ICD-O and ICD-10 codes [38]. From the Medical Births Register, we acquired individual gestational information such as birthweight, sex, and birth complications, including information on instrument-assisted delivery and cesarean section [39]. From the National Patient Register, we obtained information on maternal inpatient (1977—1993) and both inpatient and outpatient (1994 +) diagnoses, using a Danish modification of the International Classification of Diseases, ICD-8 and ICD-10 [38]. The present study included children born from 1978 to 2013. The age of diagnosis ranged from 0 to 19 years old, with year of diagnosis from 1978—2016, e.g. we included diagnoses to age 19 or to 2016, whichever came first. This resulted in 1678 cases and 39,256 controls selected from the Danish Central Person

Registry. Cases were matched to controls on birth year and sex (1:25 matching rate).

The most common pediatric CNS cancers in our sample were astrocytoma (30.9%), ependymoma (7.0%) and medulloblastoma (10.8%). Birth exposures of interest included vacuum assisted delivery, forceps assisted delivery, and any cesarean. Some mothers underwent multiple methods of delivery; for example, some had claims for both instrument-assisted delivery and cesarean section, presumably because the instrument-assisted delivery was unsuccessful. However, the number of mothers that underwent multiple interventions was not large enough to be looked at independently, thus we report risks for each intervention when it was the only one used.

Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for delivery interventions and CNS tumor. Covariates chosen were based on a review of the literature, and the final model adjusted for maternal age and birth order [2, 19, 25, 40]. We additionally considered adjustment for diabetes (gestational and/or chronic), maternal pre-pregnancy body mass index (BMI), infections during pregnancy, neurofibromatosis, tuberous sclerosis, preeclampsia, gestational hypertension, placenta praevia, placental abruption and maternal height. However, these variables did not meet the 10% change in estimate criterion [41] and were not included in final models. We additionally adjusted for maternal pregnancy smoking, which was available from 1991 to 2013, but

change in estimates remained below 10%; a study of Danish children from the same registries reported no increased risk of CNS tumors from smoking [42].

It is possible that if a brain tumor is present before birth, the fetus may have a larger head size leading to a higher probability of instrument-assisted delivery or cesarean section. Due to this possible reverse causality, we conducted a sensitivity analysis restricting diagnosis age to less than four years old and four years or older. We calculated gestational age-specific > 90th percentile head circumference, based on the international standards for fetal growth from 2006 [43]. Because children with brain tumors are more likely to be born at either high or low birthweight [4, 44], we also conducted sensitivity analyses including only infants with normal birthweight (2500—4000 g). Although maternal height and BMI were only collected during some of the study period, we conducted sensitivity analyses examining associations stratifying by mothers' stature (<165 cm/≥165 cm) and BMI (<25/≥25), because maternal height and BMI influence the use of delivery interventions [45, 46]. We additionally considered the role of plural birth, but the very small numbers of plural births meant that overall findings were very similar between all births and singleton births (results not shown).

All analyses were performed using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Demographic characteristics of cancer cases and controls were previously published [37]. The demographics of children were similar by mode of delivery (Table 1). Male children were more likely to have been born using forceps-assisted deliveries and female children were more likely to have been born by cesarean section. Birthing interventions were more likely to be used with children born first or second, compared to later births. Older mothers (35 +) were more likely to have had a cesarean section. The use of forceps declined across the study period from 8% in 1990 to < 1% in 2010.

Mean birthweight was slightly higher for those with CNS tumors and astrocytoma, compared to those without CNS tumors, and slightly lower for those with ependymoma and medulloblastoma when compared to controls (Table 2). Medulloblastoma cases had almost double the percentage of preterm birth compared to controls. The percentage of pelvic disproportion and prolonged labor among ependymoma cases was almost four times greater than the other cancers. A higher percentage of astrocytoma cases were classified to be in an abnormal fetal position than controls. Compared to controls, CNS tumor cases had a higher percentage of children with a five-minute Apgar score of less than ten.

Adjusted results revealed that ependymoma cases had 1.74 higher odds of having a vacuum assisted delivery compared to those who were birthed spontaneously (95% CI 1.02, 2.96). CNS (all types) and astrocytoma cases had an increased risk of being born by cesarean section, 1.20 (95% CI 1.06, 1.36) and 1.26 (95% CI 1.00, 1.58), respectively (Table 3).

Sensitivity analysis of age at diagnosis restriction to four years (Supplementary Table 2) showed no difference in the increased risk for ependymoma with vacuum delivery, while the association between astrocytoma and cesarean section was attenuated. Restricting to diagnosis at less than 4 years old had an increased risk for CNS and astrocytoma tumors for any cesarean section. When we conducted a sensitivity analysis restricting to cases with normal birthweight (2500—4000 g), point estimates were similar to all cases (Supplementary Table 3). Sensitivity analyses for average maternal height and BMI showed that CNS tumor cases had a higher odds of having any cesarean sections, 1.58 (95% CI 1.13, 2.22) and 1.54 (95% CI 1.05, 2.28), respectively (Supplementary Tables 4, 5). In sensitivity analysis that restricted to women of shorter height (<165 cm), CNS tumor cases' associations moved closer towards the null value (OR 1.15, 95% CI 1.00, 1.32) for any cesarean section (Supplementary Table 4).

Discussion

In this population-based case-control study using nationwide Danish registries, we found an elevated risk of vacuum assisted deliveries among ependymoma cases, and a weak increase in astrocytoma risk following cesarean section. European countries with low instrument assisted delivery rates also tend to have lower incidence of ependymoma [47, 48]. The prevalence of cesarean section (19.5%) and other modes of delivery we observed in our sample was similar to that seen in other Danish studies [21,

49]. We did not expect an increased risk of embryonal brain tumors (medulloblastoma) from instrument-related head trauma, as by definition embryonal cancers are initiated during the embryonal period prior to the birth. A larger head size may be a consequence of the tumor [50], leading to greater likelihood of need for surgical interventions during delivery. This may have introduced reverse causality into our study. However, our sensitivity analyses restricting to four years or more at age at diagnosis for brain tumors, i.e. tumors that most likely did not develop or grow until after birth, did not show a difference in estimated risk.

Prior studies on this topic suggested potential increase in risk with instrument-assisted delivery. One study reported on delivery via forceps and found an increased risk for any CNS tumor (all types grouped together) when there was also a head injury (OR=1.2, 95% CI 0.9, 1.6) [16]. Because the use of forceps was rare in our population (0.84% of births), we were unable to confirm these associations. Most other studies on this topic reported increased risk for CNS tumors, but none of these reported results specific to ependymoma [2, 16, 19, 20]. Several of these prior studies collected data via self-report [16, 19, 20], leading some authors to question whether such results may have been due to recall bias [19]. A study that relied on record linkage grouped all cancer subtypes together and found no association with vacuum and only a weak increase with forceps (OR=1.11) [2]. Notably, the one other record-linkage study that did report on vacuum extraction and ependymoma risk also showed an elevated point estimate with wide

confidence intervals (OR=1.4, 95% CI 0.4, 5.2) [34]. Thus, although prior results have not been reported in a consistent manner, our findings support that instrument-assisted delivery may result in increased ependymoma risk.

Risk for brain tumors after instrumental delivery may depend on the development of inflammation at the injury site, or may be due to cell proliferation during tissue repair, potentially leading to mutations. Tissue repair from head injuries may activate oncogenes or inactivate tumor suppressor genes [51]. Alternatively, disturbances in the blood-brain barrier resulting from injuries may make the barrier leaky and allow mutagenic substances to reach brain cells [52].

Our results also suggest an increased risk for astrocytoma with cesarean section. Yet, these findings are attenuated in sensitivity analyses, suggesting that pregnancy complications seen in children who later develop brain tumors [33, 35, 53] may in part explain elevated risks. In addition, European countries with higher rates of cesarean section do not consistently have higher incidence of astrocytoma [47, 48]. {, 1998 #4363}Prior studies have found mixed results when examining astrocytoma or “astroglial tumors” and cesarean section [20, 33, 34]. Studies assessing the impact of cesarean section on the brains of newborns have been rare, but animal studies have suggested that vaginal births may be neuroprotective by decreasing cell death across brain regions. This may be due to the vasopressin’s protective effect from excitotoxicity in the brain since vaginal

birth triggers a much larger release of vasopressin than cesarean section [54].

There was a 13.8% increase in cesarean sections in Europe from 1990 to 2014 [55]. As cesarean sections have become more common, instrument-assisted deliveries declined by 14.6% from 2004 to 2015 [21, 56]. Cesarean sections are associated with a number of complications in the newborn including hypoglycemia, respiratory distress syndrome and hyperbilirubinemia [57]. Although low by international standards, the rate we observed for cesarean section was still above optimal levels (10—15% of {, 1985 #4364}births [58]);{, 1985 #4364} nonetheless, Denmark has lower cesarean section rates than other European nations [48]. Typically, instrument-assisted deliveries are viewed as having lower risks than cesarean section, with some researchers urging a return to these deliveries [59] because complication rates remain lower than with cesarean section. However, higher rates of instrumental births do not necessarily equate to lower cesarean sections [21]. Solutions that may increase spontaneous vaginal births include external prenatal physical maneuvering for breech cases, parental education to reduce elective cesarean rates, promoting vaginal deliveries after previous cesarean section and social support interventions to diminish maternal anxieties about potential risks associated with labor [60].

A cohort study analysis of the Danish data was not feasible because Danish privacy laws prevented access to the entire cohort of Danish births.

This study did not have access to medical records to verify or extract additional information than what was provided in the Danish Registries. Yet, the use of the Danish Hospital Registry data is a strength of this study as these data are nationwide and any errors are expected to be non-differential. The free and universal health care system in Denmark, with almost full uptake of prenatal care, guarantees high coverage and validity of data elements used in our study. Certain variables, such as maternal smoking, BMI, and height were collected for only part of the study period, thus limiting our ability to adjust for these variables. However, in sensitivity analysis, height and obesity did not change observed risk estimates. Maternal smoking is not expected to act as a predictor of childhood brain tumor risk [42]. Furthermore, breech presentation was not present in the registries, which may be a relevant cofactor in cesarean risk, nor was breastfeeding available, which may impact cancer risk. Abnormal fetal position was not broken down by type, such as breech, face, brow presentation, as that information was not available. Length of delivery was also not present in the database. Results must be taken in light of multiple comparisons in this study.

In summary, we found increased risk for ependymomas with vacuum-assisted delivery. The literature on this topic has been inconsistent in examining brain tumor subtypes and instrument types. Pooling data on this topic may provide better statistical power for additional subgroup analyses. Further studies on the pathophysiology need to be conducted, but if these

hypotheses are found to be true, reducing instrument assisted deliveries may be an actionable strategy to reduce childhood brain tumor risk. Nonetheless, childhood brain tumors are rare, and thus the absolute risk is low from these modes of delivery.

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Table 1: Demographics of the Danish registry population cases and controls (<20 years) by modes of delivery (births 1978—2013 and diagnosed 1978—2016)[a].

	Spontaneous Delivery	Forceps	Vacuum	Any Cesarean Section
Total N= 40,934 N(%)[b]	28,268 (69.1)	343 (0.8)	4,339 (10.6)	7,984 (19.5)
Child's Sex N(%)				
Male	14,520 (51.4)	192 (56.0)	2,252 (51.9)	3,575 (44.8)
Female	13,748 (48.6)	151 (44.0)	2,087 (48.1)	4,409 (55.2)
Birthweight N(%)				
Low (≤2449)	869 (3.1)	14 (4.1)	124 (2.9)	965 (12.1)
Normal (2500-4000)	22,580 (80.0)	283 (82.5)	3,427 (79.0)	5,718 (71.6)
High (4000+)	4,716 (16.7)	45 (13.1)	781 (18.0)	1,264 (15.8)
Missing	103	1	7	37
Maternal Age N(%)[c]				
≤ 24	6,623 (23.4)	97 (28.3)	1,134 (26.1)	1,490 (18.7)
25-29	10,873 (38.5)	119 (34.7)	1,676 (38.6)	2,785 (34.9)
30-34	7,767 (27.5)	93 (27.1)	1,090 (25.1)	2,457 (30.8)
35+	3,005 (10.6)	34 (9.9)	439 (10.1)	1,252 (15.7)
Birth Order N(%)[c]				
1	10,835 (38.3)	135 (39.4)	2,999 (69.1)	3,374 (42.3)
2	11,448 (40.5)	136 (39.7)	1,016 (23.4)	2,858 (35.8)
3	4,454 (15.8)	50 (14.6)	263 (6.1)	1,283 (16.1)
4+	1,531 (5.4)	22 (6.4)	61 (1.4)	469 (5.9)
Age of Diagnosis N(%)				
0 - 4	8,944 (31.6)	88 (25.7)	1,371 (31.6)	2,903 (36.3)
5 - 9	8,132 (28.8)	91 (26.5)	1,309 (30.2)	2,323 (29.1)
10 - 14	5,865 (20.8)	80 (23.3)	912 (21.0)	1,529 (19.2)
15 - 19	5,327 (18.8)	84 (24.5)	747 (17.2)	1,229 (15.4)
Gestational Age N(%)				
Very Preterm Birth (≤32 weeks)	130 (0.5)	<5	8 (0.2)	242 (3.0)
Preterm Birth (33 to 36 weeks)	905 (3.2)	13 (3.8)	131 (3.0)	713 (8.9)
Term Birth (37+ weeks)	26,292 (93.0)	317 (92.4)	4,020 (92.6)	6,763 (84.7)
Missing	941	10	180	266
Head circumference (mean; cm)	35.1 (1.8)	35.1 (1.3)	35.4 (1.8)	35.0 (2.4)
Head circumference >90th Percentile N(%)	3,393 (12.0)	11 (3.2)	623 (14.4)	1,938 (24.3)
Maternal Smoking N(%)[d]				
Yes	3,838 (13.6)	30 (8.8)	524 (12.1)	1,383 (17.3)
No	11,398 (40.3)	53 (15.5)	1,846 (42.5)	4,167 (52.2)
Missing	663	5	86	346
Maternal Height N(%)[e]				
163 cm or less	761 (17.8)	<5	154 (18.6)	505 (22.9)
164-168 cm	928 (21.8)	<5	215 (26.0)	522 (23.7)
169-172 cm	787 (18.5)	5 (50.0)	141 (17.1)	388 (17.6)
173 cm+	858 (20.1)	<5	144 (17.4)	350 (15.9)
Missing	932	<5	173	441
Maternal BMI N(%)[e]				
Underweight (<18.5)	161 (3.8)	<5	29 (3.5)	55 (2.5)
Normal weight (18.5-24.99)	2,167 (50.8)	5 (50.0)	408 (49.3)	947 (42.9)
Overweight (25-29.99)	611 (14.3)	<5	120 (14.5)	441 (20.0)
Obese (>30)	345 (8.1)	<5	86 (10.4)	289 (13.1)
Missing	982	<5	184	474

Gestational Diabetes N(%)[f]				
Yes	154 (1.2)	<5	26 (1.3)	148 (2.9)
No	12,360 (98.8)	46 (95.8)	2,032 (98.7)	4,987 (97.1)
Pre-pregnancy Diabetes N(%)				
Yes	32 (0.3)	<5	6 (0.3)	79 (1.5)
No	12,482 (99.7)	48 (100.0)	2,052 (99.7)	5,056 (98.5)
Neurofibromatosis N(%)				
Yes	55 (0.2)	<5	5 (0.12)	24 (0.3)
No	28,253 (99.9)	342 (99.7)	4,334 (99.9)	7,960 (99.7)

[a] This table is limited to mothers exposed to one intervention only.
[b] Total N is the sum of spontaneous delivery, forceps, vacuum and cesarean section.
[c] There was no missing in this variable.
[d] Maternal smoking information was available from 1991-2013.
[e] Maternal height and maternal BMI information was available from 2003-2013.
[f] Gestational diabetes information available from 1994-2013.

Table 2. Pregnancy and labor characteristics of brain tumor cases and controls for children (<20 years; births 1978—2013 and diagnoses 1978—2016).

	Controls (N=39,256)	**CNS Tumors** (N=1,678)	**Astrocytoma** (N=518)	**Ependymoma** (N=118)	**Medulloblastoma** (N=181)
Gestational factors					
Maternal Age[1]					
≤24	8,971 (22.9)	373 (22.2)	131 (25.3)	31 (26.3)	38 (21.0)
25-29	14,793 (37.7)	660 (39.3)	198 (38.2)	46 (39.0)	77 (42.5)
30-34	10,937 (27.8)	470 (28.0)	143 (27.6)	27 (22.9)	39 (21.5)
35+	4,555 (11.6)	175 (10.5)	46 (8.9)	14 (11.8)	27 (15.0)
Birth Order[1]					
1	16,646 (42.4)	697 (41.5)	226 (43.6)	54 (45.8)	80 (44.2)
2	14,820 (37.8)	638 (38.0)	188 (36.3)	42 (35.6)	69 (38.1)
3	5,787 (14.7)	263 (15.7)	79 (15.3)	17 (14.4)	26 (14.4)
4+	2,003 (5.1)	80 (4.8)	25 (4.8)	5 (4.2)	6 (3.3)
Child's Sex[1]					
Male	19,712 (50.2)	827 (49.3)	237 (45.8)	66 (55.9)	106 (58.6)
Female	19,544 (49.8)	851 (50.7)	281 (54.2)	52 (44.1)	75 (41.4)
Birthweight (g)[1]	3,444.9 (580.4)	3,480.7 (608.8)	3,472.7 (602.4)	3,433.1 (575.4)	3,362.4 (650.8)
Low (≤2449)	1,880 (4.8)	92 (5.5)	31 (6.0)	6 (5.1)	16 (8.8)
Normal (2500-4000)	30,768 (78.4)	1,240 (73.9)	380 (73.4)	93 (78.8)	137 (75.7)
High (4000+)	6,466 (16.5)	340 (20.3)	106 (20.5)	18 (15.3)	28 (15.5)
Missing	142	6	<5	<5	-
Gestational age (weeks)[2]	39.5 (1.8)	39.4 (1.9)	39.5 (1.8)	39.4 (2.0)	39.0 (2.4)
Very Preterm Birth (≤32 weeks)[1]	364 (0.9%)	19 (1.1%)	5 (1.0%)	<5	<5
Preterm Birth (33 to 36 weeks)[1]	1,691 (4.3%)	71 (4.2%)	21 (4.1%)	<5	15 (8.3%)
Term Birth (37+ weeks)[1]	35,858 (91.3%)	1,534 (94.5%)	462 (89.2%)	109 (92.4%)	159 (87.8%)
Head circumference (cm)[2]	35.1 (1.9)	35.1 (2.0)	35.2 (1.7)	35.0 (1.8)	34.6 (2 .3)
Head circumference >90th Percentile[1]	5722 (14.6%)	243 (14.5%)	65 (12.5%)	10 (8.5%)	33 (18.2%)
1-minute Apgar score[2]	9.33 (1.36)	9.32 (1.40)	9.32 (1.23)	9.23 (1.37)	9.24 (1.87)
1-minute Apgar score <7[1]	1,000 (2.6%)	45 (2.7%)	13 (2.5%)	<5	6 (3.3%)
5-minute Apgar score[2]	9.86 (0.72)	9.85 (0.77)	9.87 (0.67)	9.79 (0.91)	9.85 (0.71)
5-minute Apgar score <10[1]	1,411 (3.6%)	70 (4.2%)	26 (5.0%)	7 (5.9%)	6 (3.3%)
Risk factors for Instrument-assisted Vaginal Delivery or Cesarean Section					
Threatened fetal death[1]	268 (0.7%)	15 (0.9%)	5 (1.0%)	<5	<5
Pelvic disproportion[1]	444 (1.1%)	21 (1.3%)	6 (1.2%)	5 (4.2%)	<5
Abnormal fetal position[1]	1,376 (3.5%)	60 (3.6%)	29 (5.6%)	<5	<5
Prolonged labor for other reasons[1]	878 (2.2%)	33 (2.0%)	8 (1.5%)	5 (4.2%)	<5
Any of the above risk factors[1,3]	2,685 (6.8%)	121 (7.2%)	47 (9.1%)	11 (9.3%)	9 (5.0 %)

Primipara[1]	11,171 (28.5%)	503 (30.0%)	172 (33.2%)	41 (34.8%)	60 (33.2%)

[1] N (%)
[2] Mean (standard deviation)
[3] Any one or more of the above risk factors

Table 3: Odds Ratios for brain tumor risk and mode of delivery for children (<20 years; births 1978—2013 and diagnoses 1978—2016).

	Vacuum		Forceps		Cesarean section	
	Cases N(%)	OR[a]	Cases N(%)	OR[a]	Cases N(%)	OR[a]
CNS tumors	168 (10.0)	0.99 (0.84, 1.18)	19 (1.1)	1.26 (0.78, 2.03)	370 (22.1)	1.20 (1.06, 1.36)
Astrocytoma	63 (12.2)	1.19 (0.89, 1.58)	<5	---	108 (20.9)	1.26 (1.00, 1.58)
Ependymoma	20 (17.0)	1.74 (1.02, 2.96)	<5	---	18 (15.3)	0.90 (0.52, 1.54)
Medulloblastoma	16 (8.8)	0.90 (0.52, 1.55)	<5	---	44 (24.3)	1.26 (0.87, 1.82)

[a] Models adjust for maternal age and birth order.

Supplementary Tables

Supplementary Table 1: Danish ICD-10 Codes used to identify modes of delivery

Vacuum Assisted Delivery	KMAE00, KMAE03, KMAE20, KMAE96, KMAE99, O814
Forceps Assisted Delivery	KMAF00, KMAF10, KMAF20, O810, O811, O812, O813
Spontaneous Delivery	O80, O800, O801, O802, O803, O808, O809, O840
Cesarean Section	KMCA00, KMCA10, O828, O829, O82, KMCA10A, KMCA10C, KMCA10D, KMCA10E, KMCA12, KMCA12A, KMCA12B, O21, O821A, O821B, O821C, O822, O843, O843A, O843B, O843C, KMCA10B, KMCA11, KZYM00, O842, O820

Supplementary Table 2: Sensitivity analysis for odds ratios of childhood brain tumor risk and modes of delivery, stratifying by age at diagnosis

	Age at Diagnosis <4 Years Old						**Age at Diagnosis 4+ Years Old[1]**			
	Forceps		**Vacuum**		**Cesarean Section**		**Vacuum**		**Cesarean Section**	
	Cases N(%)	OR[2]	Cases N(%)	OR[2]	Cases N(%)	OR[2]	Cases N(%)	OR[2]	Cases N(%)	OR[2]
CNS	5 (0.3)	1.59 (0.62, 4.07)	50 (3.0)	1.17 (0.85, 1.60)	126 (7.5)	1.45 (1.16, 1.82)	118 (7.0)	0.94 (0.76, 1.15)	244 (14.5)	1.11 (0.95, 1.29)
Astrocytoma	<5	--	17 (3.3)	1.41 (0.80, 2.46)	36 (6.9)	1.65 (1.08, 2.51)	46 (8.9)	1.12 (0.80, 1.56)	72 (13.9)	1.13 (0.85, 1.49)
Ependymoma	<5	--	11 (9.3)	1.85 (0.88, 3.90)	11 (9.3)	1.00 (0.49, 2.06)	9 (7.6)	1.79 (0.82, 3.90)	7 (5.9)	0.80 (0.34, 1.86)
Medulloblastoma	<5	--	6 (3.3)	1.02 (0.41, 2.53)	18 (9.9)	1.54 (0.83, 2.83)	10 (5.5)	0.84 (0.42, 1.67)	26 (14.4)	1.13 (0.71, 1.81)

[1] Sample size was too small to examine forceps assisted deliveries.
[2] Models adjust for maternal age and birth order.

Supplementary Table 3: Sensitivity analysis for odds ratios of childhood brain tumor risk and modes of delivery, restricting to normal birthweights (2500-4000g)

	Vacuum		**Forceps**		**Cesarean Section**	
	Cases N(%)	OR[1]	Cases N(%)	OR[1]	Cases N(%)	OR[1]
CNS	117 (7.0)	0.90 (0.74, 1.11)	15 (0.9)	1.25 (0.72, 2.15)	248 (14.8)	1.15 (0.98, 1.33)
Astrocytoma	44 (8.5)	1.13 (0.81, 1.60)	<5	---	75 (14.5)	1.31 (0.99, 1.72)
Ependymoma	12 (10.2)	1.32 (0.68, 2.56)	<5	---	12 (10.2)	0.76 (0.39, 1.48)
Medulloblastoma	14 (7.7)	1.06 (0.58, 1.94)	<5	---	33 (18.2)	1.27 (0.83, 1.96)

[1] Models adjust for maternal age and birth order.

Supplementary Table 4: Sensitivity analysis for odds ratios of childhood brain tumor risk and modes of delivery, stratifying by average maternal height (≥165cm)[1] or short maternal height (<165cm)

	Average Maternal Height (≥165cm)[1]				**Short Maternal Height (<165cm)**					
	Vacuum		**Cesarean Section**		**Vacuum**		**Forceps**		**Cesarean Section**	
	Cases N(%)	OR[2]	Cases N(%)	OR[2]	Cases N(%)	OR[2]	Cases N(%)	OR[2]	Cases N(%)	OR[2]
CNS	17 (1.0)	1.10 (0.64, 1.91)	66 (3.9)	1.58 (1.13, 2.22)	151 (9.0)	0.97 (0.81, 1.17)	19 (1.1)	1.29 (0.80, 2.07)	304 (18.1)	1.15 (1.00, 1.32)
Astrocytoma	7 (1.4)	2.19 (0.86, 5.56)	13 (2.57)	1.40 (0.66, 3.00)	56 (10.8)	1.13 (0.83, 1.52)	<5	---	95 (18.3)	1.25 (0.98, 1.60)
Ependymoma	<5	---	<5	---	18 (15.3)	1.74 (0.99, 3.08)	<5	---	15 (12.7)	0.86 (0.47, 1.55)
Medullblastoma	<5	---	8 (4.4)	1.99 (0.75, 5.29)	15 (8.3)	0.88 (0.50, 1.57)	<5	---	36 (19.9)	1.14 (0.76, 1.72)

[1] The number of forceps assisted deliveries was too small to run sensitivity analyses.
[2] Models adjust for maternal age and birth order.

Supplementary Table 5: Sensitivity analysis for odds ratios of childhood brain tumor risk and modes of delivery, stratifying by normal maternal BMI (≤25)[1] or high maternal BMI (>25)[1,2]

	Normal Maternal BMI (≤25)				**High Maternal BMI (>25)**			
	Vacuum		**Cesarean section**		**Vacuum**		**Cesarean Section**	
	Cases N(%)	OR	Cases N(%)	OR	Cases N(%)	OR	Cases N(%)	OR
CNS	19 (1.1)	1.49 (0.87, 2.56)	47 (2.8)	1.54 (1.05, 2.28)	9 (0.5)	0.88 (0.39, 2.00)	35 (2.1)	1.07 (0.65, 1.75)
Astrocytoma	7 (1.4)	2.38 (0.91, 6.23)	8 (1.5)	0.96 (0.39, 2.33)	<5	---	7 (1.4)	1.04 (0.35, 3.07)
Medulloblastoma	<5	---	7 (3.9)	1.46 (0.51, 4.14)	<5	---	6 (3.3)	3.08 (0.66, 14.48)

[1]The number of forceps assisted deliveries was too small to run sensitivity analyses. Models adjust for maternal age and birth order
[2]The sample size of ependymoma was too small for this analysis.