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Research Article

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Fetal Growth, Preterm Birth, Neonatal Stress and Risk for CNS Tumors in Children: A Nordic Population- and Register-Based Case-Control Study

Lisbeth Samsø Schmidt[1], Joachim Schüz[1], Päivi Lähteenmäki[3], Catarina Träger[4], Tore Stokland[5], Göran Gustafson[4], Lisa Hjalgrim[6], Astrid Sehested[6], Christoffer Johansen[1], and Kjeld Schmiegelow[6,2]

Abstract

Background: The peak incidence of central nervous system (CNS) tumors in childhood indicates that intrauterine or neonatal characteristics are potential risk factors or symptoms of early onset of disease.

Methods: We conducted a registry-based case-control study nested in the childhood populations of Denmark, Finland, Sweden, and Norway on the association between indicators of fetal growth and neonatal stress and childhood CNS tumor risk diagnosed during the period 1985-2006. Each of the 3,443 cases was matched individually on date of birth, sex, and country to five controls sampled randomly from population registries. Information on birth characteristics was obtained from national birth registries. We estimated odds ratios (OR) and 95% confidence intervals (95% CI) by conditional logistic regression analyses.

Results: We observed a U-shaped relation between risk for CNS tumors and birthweight, at >4.5 kg (OR, 1.27; 95% CI, 1.03-1.55) and <2.0 kg (OR, 1.50; 95% CI, 1.13-1.99), the latter being attenuated after adjustment for gestational age. Moreover, small-for-gestational age (OR, 1.28; 95% CI, 0.98-1.66) and large-for-gestational age (OR, 1.26; 95% CI, 1.02-1.55) were both associated with CNS tumors. The OR for preterm births was increased per 1-week decrease in gestational age (OR, 1.58; 95% CI, 1.04-2.44). Increased ORs were also observed for head circumference >38 cm (1.80; 95% CI, 1.18-2.74), 5-minute Apgar score <7 (1.44; 95% CI, 0.98-2.12), and breech presentation (1.33; 95% CI, 1.04-1.69). The observed associations varied little by histologic subgroup.

Conclusions: This study supports intrauterine or neonatal onset of childhood CNS tumors. The findings provide insight into the natural history of childhood CNS tumors indicating an early onset or, alternatively, potentially harmful exposures in the neonatal period that might be preventable. *Cancer Epidemiol Biomarkers Prev; 19(4); 1042–52. ©2010 AACR.*

Introduction

Childhood central nervous system (CNS) tumors are a group of biologically and clinically distinct diseases, each with its own epidemiology, grade of malignancy, and cytogenetic and molecular aberrations (1). Accordingly, certain genetic syndromes, such as neurofibromatosis, tuberous sclerosis, and Turcot syndrome, each predisposes to specific histologic subgroups of CNS tumors (1, 2). The only well-established environmental risk factor is ionizing radiation (3). Thus, for the vast majority of CNS tumors in previously healthy children the etiology is unknown. As an age-associated incidence peak is observed in childhood (4), prenatal and perinatal characteristics are potential risk factors and/or symptoms of early onset of the disease. In addition, preterm and low-birth-weight infants and those with a low Apgar score often undergo intensive neonatal care (ref. 5; involving, e.g., X-rays, oxygen treatment), and their immature or impaired blood-brain barrier makes their brains particularly vulnerable to infectious agents and cytotoxic drugs.

Preterm birth and various indicators of neonatal stress have been investigated in small studies, with inconclusive results (6-15). The hypothesis that increased risk for CNS tumors (16) and other cancers (17, 18) are associated with high birth weight is supported by numerous studies. More precise estimates of growth, however, such as

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Table 1. Eligible patients with CNS tumors by age, sex, and histology

Histology	0-4 y		5-9 y		10-14 y		0-14 y			%
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	All	
Ependymoma	106	93	55	34	36	30	197	157	354	10
Astrocytoma	288	284	253	231	204	196	745	711	1,456	42
Embryonal CNS tumors	159	124	145	89	70	42	374	255	629	18
Other gliomas	47	37	54	64	35	43	136	144	280	8
Other specified CNS tumors	70	53	85	69	106	82	261	204	465	14
Unspecified CNS tumors	53	42	55	38	36	35	144	115	259	8
Total	723	633	647	525	487	428	1,857	1,586	3,443	100

NOTE: Classified according to the International Classification of Childhood Cancer version 3.

birth weight by gestational age, have not been associated with CNS tumors in previous studies (19, 20). Increased head circumference was shown to be associated with CNS tumors independently of birth weight in case series and in a cohort study (21, 22), which may indicate that the tumor was present at birth and not induced by fetal growth.

To examine further the associations with intrauterine growth, birth weight, head circumference, preterm birth, breech presentation, Apgar score, and the risks for histologically defined subgroups of childhood CNS tumors, we conducted a large population-based case-control study nested in the Danish, Norwegian, Swedish, and Finnish childhood populations. The study was based on information from the high-quality population-based administrative health registers of the Nordic countries on 3,983 CNS tumor cases diagnosed between 1985 and 2006.

Methods

All citizens of the Nordic countries are assigned a unique personal identification number at either birth or when moving into the country, and this number contains information about date of birth and sex. This system enables identification of all citizens on an individual level, and the personal identification number is used in all national administrative registries, allowing an optimal record linkage between registries. All children ages 0 to 14 y in whom a primary CNS tumor was diagnosed between January 1, 1985 and December 31, 2006, who had resided in Denmark, Norway, Sweden, or Finland at the time of diagnosis, were identified in the national cancer registries, which are nationwide and continuously updated and in which registration from various sources such as hospitals and pathologies is mandatory by law (23). In Sweden and Denmark cases were additionally identified in the independent childhood cancer registries, and, for the Norwegian cases, in the solid-tumor database of the Nordic Society of Pediatric Hematology and Oncology, but only resulting in the identification of 20 additional cases. Diagnostic information on the Swedish (24) and most of the Danish cases (25) was reabstracted and recoded on the basis of information from the medical records. In Finland, pathology reports were consulted to classify the tumors more specifically than in the data available from the Finnish Cancer Registry. CNS tumors were defined according to main group III of the International Classification of Childhood Cancer, 3rd edition (26). Each case was individually matched by date of birth (birth month and year), sex, and country to five controls identified randomly from the annual Nordic population of approximately 4.4 million children 0 to 14 y old. Controls were identified in national population registries and had to be alive, to have no previous diagnosis of childhood solid tumor, and to have been living in the country at the time of diagnosis of the corresponding case.

Information on the birth characteristics of cases and controls was obtained from the population-based medical birth registries (27) in Denmark (established 1973), Norway (established 1967), Finland (established 1987), and Sweden (established 1973), which contain mandatory, continuously updated reports on all births in these countries. The registries were linked by the unique personal identification numbers assigned to all citizens of the Nordic countries.

We identified 3,983 children with a diagnosed primary CNS tumor. Of these, 362 were born before establishment of the birth registries and 178 were not born in their country of residence, leaving 3,443 eligible cases with information recorded in the medical birth registries. Of the 17,178 matched controls, 1,009 were born outside the country of residence, leaving 16,169 eligible controls.

We studied the associations with birth weight, gestational age, birth weight for gestational age, Apgar score 5 min after birth, breech presentation, and head circumference. Gestational age was measured as completed weeks of gestation, which in the early period was primarily determined by the date of the last menstrual period and in later years by ultrasound in early pregnancy. This change happened gradually over time. We did not have information about the method of determining gestational age on an individual level for the entire

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Table 2. Birth weight and CNS tumors by histologic subgroup

Birth weigh (g)	Conditional OR*			OR† adjusted for GA		
	No. cases	No. controls	OR* (95% CI)	No. cases	No. controls	OR† (95% CI)
All CNS tumors	3,426	16,039		3,349	15,359	
<2,000	66	222	1.50 (1.13-1.99)	61	203	1.15 (0.81-1.65)
2,000-2,500	99	436	1.13 (0.90-1.42)	99	414	1.05 (0.82-1.34)
2,500-3,000	390	1,784	1.09 (0.96-1.24)	382	1,697	1.06 (0.93-1.21)
3,000-3,500	1,013	5,090	1.00 (referent)	991	4,882	1.00 (referent)
3,500-4,000	1,173	5,608	1.05 (0.96-1.15)	1,150	5,386	1.07 (0.97-1.17)
4,000-4,500	552	2,371	1.17 (1.05-1.32)	536	2,272	1.20 (1.07-1.35)
>4,500	133	528	1.27 (1.03-1.55)	130	505	1.32 (1.07-1.62)
Ependymoma	352	1,661		344	1,592	
<2,000	7	23	1.65 (0.69-3.94)	7	20	1.98 (0.69-5.67)
2,000-2,500	14	39	1.89 (0.99-3.62)	14	36	2.07 (1.04-4.15)
2,500-3,000	34	190	0.93 (0.61-1.41)	34	179	0.99 (0.64-1.54)
3,000-3,500	98	514	1.00 (referent)	94	499	1.00 (referent)
3,500-4,000	131	611	1.13 (0.85-1.50)	129	587	1.16 (0.87-1.56)
4,000-4,500	55	219	1.33 (0.92-1.93)	53	212	1.33 (0.90-1.96)
>4,500	13	65	1.05 (0.56-1.98)	13	59	1.17 (0.61-2.24)
Astrocytoma	1,450	6,779		1,419	6,532	
<2,000	29	82	1.74 (1.12-2.69)	24	77	1.11 (0.64-1.95)
2,000-2,500	38	190	1.00 (0.69-1.43)	38	183	0.89 (0.60-1.30)
2,500-3,000	153	714	1.06 (0.86-1.30)	151	686	1.02 (0.83-1.26)
3,000-3,500	440	2,184	1.00 (referent)	433	2,113	1.00 (referent)
3,500-4,000	505	2,402	1.04 (0.91-1.20)	494	2,310	1.07 (0.93-1.24)
4,000-4,500	238	1,006	1.18 (0.99-1.41)	233	970	1.22 (1.02-1.47)
>4,500	47	201	1.16 (0.83-1.63)	46	193	1.22 (0.87-1.72)
Embryonal CNS tumors	629	2,961		614	2,829	
<2,000	13	42	1.61 (0.84-3.07)	13	39	1.26 (0.56-2.87)
2,000-2,500	15	74	1.01 (0.57-1.79)	15	71	0.91 (0.49-1.67)
2,500-3,000	67	331	1.01 (0.74-1.37)	64	313	0.95 (0.69-1.31)
3,000-3,500	185	934	1.00 (referent)	183	889	1.00 (referent)
3,500-4,000	218	1,000	1.10 (0.88-1.36)	214	957	1.09 (0.87-1.36)
4,000-4,500	98	487	1.01 (0.77-1.32)	93	470	0.99 (0.74-1.31)
>4,500	33	93	1.80 (1.18-2.77)	32	90	1.81 (1.16-2.81)
Other glioma	277	1,281		266	1,200	
<2,000	4	20	1.16 (0.39-3.50)	4	19	1.04 (0.28-3.84)
2,000-2,500	6	35	0.98 (0.40-2.40)	6	33	0.97 (0.37-2.51)
2,500-3,000	42	135	1.77 (1.15-2.71)	39	126	1.69 (1.08-2.66)
3,000-3,500	72	413	1.00 (referent)	70	387	1.00 (referent)
3,500-4,000	96	455	1.21 (0.86-1.69)	93	426	1.22 (0.86-1.72)
4,000-4,500	45	178	1.44 (0.96-2.19)	43	165	1.43 (0.93-2.19)
>4,500	12	45	1.49 (0.76-2.95)	11	44	1.39 (0.68-2.85)
Other specified CNS	460	2,148		452	2,058	
<2,000	7	39	0.84 (0.37-1.90)	7	32	0.73 (0.27-1.96)
2,000-2,500	13	66	0.88 (0.47-1.64)	13	61	0.80 (0.41-1.56)
2,500-3,000	54	256	0.96 (0.68-1.36)	54	245	0.94 (0.65-1.35)
3,000-3,500	143	652	1.00 (referent)	139	622	1.00 (referent)
3,500-4,000	145	734	0.90 (0.70-1.16)	142	716	0.91 (0.70-1.18)
4,000-4,500	75	316	1.09 (0.79-1.49)	74	300	1.17 (0.84-1.62)
>4,500	23	85	1.22 (0.74-2.02)	23	82	1.32 (0.79-2.19)

(*Continued on the following page*)

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Table 2. Birth weight and CNS tumors by histologic subgroup (Cont'd)

Birth weigh (g)	Conditional OR*			OR† adjusted for GA		
	No. cases	No. controls	OR* (95% CI)	No. cases	No. controls	OR† (95% CI)
Unspecified CNS	258	1,209		254	1,148	
<2,000	6	16	2.08 (0.80-5.46)	6	16	1.30 (0.40-4.26)
2,000-2,500	13	32	2.17 (1.08-4.36)	13	30	1.86 (0.86-4.01)
2,500-3,000	40	158	1.36 (0.89-2.08)	40	148	1.29 (0.83-2.01)
3,000-3,500	75	393	1.00 (referent)	72	372	1.00 (referent)
3,500-4,000	78	406	1.00 (0.71-1.40)	78	390	1.04 (0.73-1.47)
4,000-4,500	41	165	1.33 (0.87-2.03)	40	155	1.43 (0.92-2.23)
>4,500	5	39	0.66 (0.25-1.73)	5	37	0.73 (0.28-1.93)

NOTE: Classified according to the International Classification of Childhood Cancer version 3. Birth weight was available for >99% and gestational age for >97%, of the cases and controls in the periods when data were recorded.

*Conditional OR adjusted for matching factors of country, sex, and age (year and month).

†OR adjusted for matching factors of country, sex, age (year and month), and gestational age in completed weeks.

dataset, thus we carried out a sensitivity analysis. We saw no difference in risk estimates of the association between gestational age and CNS tumor between children born in the early period compared with later (data not shown). Fetal growth was estimated from birth weight by gestational age (28). Most growth curves are based on cross-sectional data on birth weight by gestational age based on the weight of newborns, but these curves do not necessarily reflect the normal intrauterine growth velocity, especially not in the preterm period when much of the data are for abnormal deliveries. We decided to estimate the deviations from the expected birth weight by gestational age by using fetal growth charts based on ultrasonically estimated fetal weights of infants subsequently born at term, for a combined Danish and Swedish cohort (29). Infants were considered to be small for gestational age (SGA) when their birth weight was <-2 SD of the expected birth weight for gestational age, and large for gestational age (LGA) when their birth weight was >+2 SD. The reference group was defined as appropriate for gestational age (AGA), within 2 SD of the expected birth weight for gestational age. We calculated the SD of the mean from our own control sample. In the categorical analyses, we used cutoffs for birth weight (<2.5 kg and >4 kg) and Apgar score (<7) from previous studies or as in the contextual definition [SGA/LGA/AGA; gestational age (term ≥37 wk, or preterm <37 wk); breech or not breech]. Due to the large dataset we also used a finer categorization for birth weight to investigate associations in more extreme categories.

Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) with the PHREG procedure in SAS (version 9.1). We examined the dose-response relation between birth weight and risk for CNS tumors in two ways: categorization of birth weight into 500-g categories and use of a quadratic-logistic spline model with predefined knots at 2.5 and 4 kg, aligned with the categorical analyses (30). Dose-response relations for gestational age were investigated in a log-linear model.

In all the conditional analyses, we accounted for country, sex, and age by keeping the individual matching. Further adjustment was based on *a priori* knowledge of potential confounders. The analyses of gestational age and birth weight were mutually adjusted. Birth order and maternal age were regarded as potential confounders for birth weight and gestational age, but, as their inclusion in the regression models changed the effect estimates only marginally (data not shown), they were not included in the final models.

As we found no variation in the associations by country, only the combined results are shown. Head circumference (n = 2,052 cases), 5-min Apgar score (n = 2,683 cases), and breech presentation (n = 1,947 cases) were available for only a subset of the data, as this information was included in the registries later in the study period or not recorded in all countries. No significant change in the estimates was seen when the birth-weight analyses were restricted to children for whom information on all the variables was available; however, the confidence intervals became wider due to decreasing numbers of children. As analysis exclusively for singletons did not change the estimates (data not shown), multiple births were included in all the analyses. Age groups of 0-4, 5-9, and 10-14 y were applied to be able to compare our results with previous studies. However, as the investigated factors in the present study were more likely to represent reverse causality if the child was diagnosed at a very young age, we chose to include another subgroup to analyze children <1 y old at diagnosis.

The study was approved by the national data protection boards of all four countries and by ethical committees in accordance with national laws and regulations.

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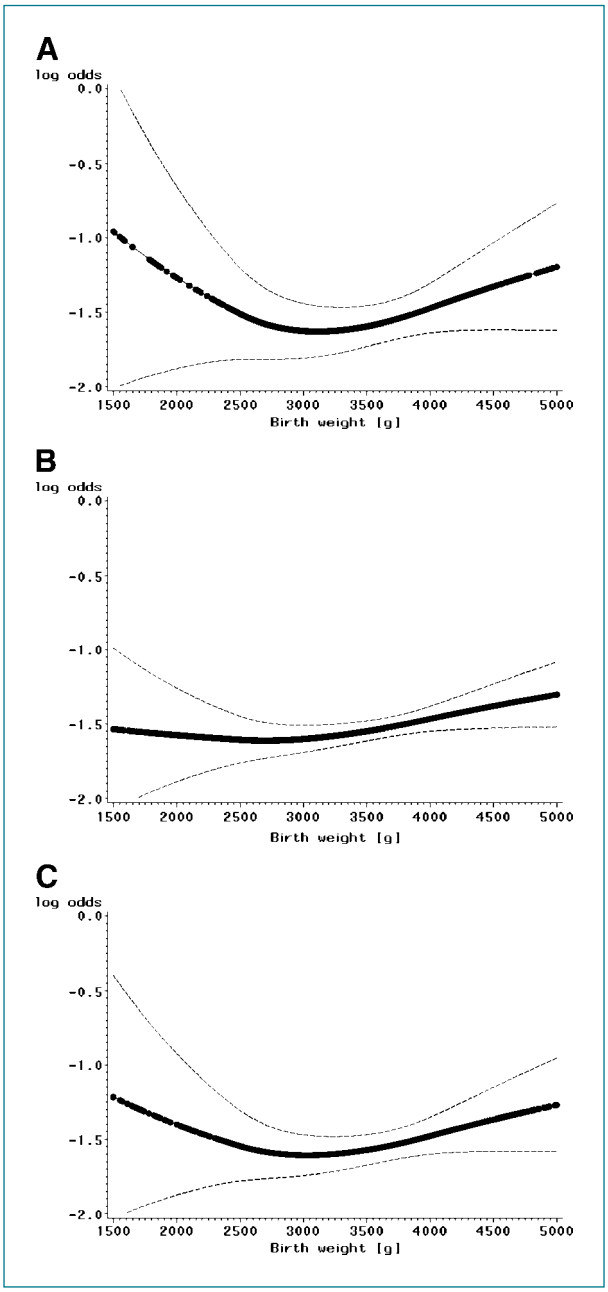

Figure 1. A to C, the dose-response relation between birth weight and risk for ependymoma, astrocytoma, and embryonal CNS tumors by applying a quadratic-logistic spline model with predefined knots at 2.5 and 4 kg (36). A, birth weight and risk for ependymoma (adjusted for gestational age). B, birth weight and risk for astrocytoma (adjusted for gestational age). C, birth weight and risk for embryonal CNS tumors (adjusted for gestational age).

Results

The distributions by age, sex, and histologic type of CNS tumor for the 3,443 eligible patients were similar in the four countries and were consistent with previous reports (Table 1).

Birth weight was associated with an increased risk for childhood CNS tumor in a U-shaped relation, i.e., increased effect estimates were observed with both lower and higher birth weights (Table 2). After adjustment for gestational age, however, the association with low birth weight was weaker, whereas the association for the high-birth-weight category remained unchanged.

When the data were stratified by histologic type and adjusted for gestational age, a similar pattern was found for nearly all the histologic subgroups. For children in the highest birth weight category (>4.5 kg), the highest OR was observed for embryonal CNS tumors. A spline model confirmed the U-shaped relations with astrocytoma, embryonal CNS tumors, and ependymoma, the three most common types of CNS tumor in children. The association with embryonal CNS tumors seemed to be more pronounced at very high birth weights (>4.5 kg after adjustment for gestational age), whereas for astrocytoma and ependymoma the association was seen at around 4 kg and was less steep at higher birth weights (Fig. 1A-C). However, the small differences by histology may be a chance finding due to small numbers.

In general, no marked differences by age at diagnosis were observed when analyzing the association between birth weight and CNS tumors (Table 3). In the investigation of the association with growth velocity by categorical analysis, an increased risk for CNS tumors was seen with both SGA and LGA, with approximately 30% increases. No variation by age at diagnosis was seen for infants who were LGA, but the association with SGA was strongest in the first year of life, with an OR of 2.62 (95% CI, 1.03-6.70).

An association was observed between large head circumference (>38 cm) and CNS tumors, which was statistically significant for all age groups <10 years. The strongest association was observed for a diagnosis of CNS tumor within the first year of life (Table 3), with a 7-fold increase in the OR, but this estimate was based on small numbers. In the categorical analysis, CNS tumors were associated with preterm birth. Furthermore, for preterm children, we observed a trend (OR, 1.58; 95% CI, 1.04-2.44) for increased risk with each week of shorter gestational age. The association with preterm birth was suggested to be strongest for the youngest age groups. An Apgar score <7 at 5 minutes was also associated with a higher risk for CNS tumors compared with children with a higher score. After stratification by age, the association was suggested to be strongest in the youngest age group (0-4 years) (Table 3).

The risk for CNS tumors was significantly higher, by 33%, for breech presentation than for other presentations. The strongest association was seen in the younger age groups, although the effect estimates were imprecise due to small numbers.

In analysis by histologic subtypes we identified few differences in the associations with fetal growth, preterm birth, Apgar score, and breech presentation (Table 4 and Supplementary Appendix). Among LGA and SGA children the highest risk estimates were observed for

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embryonal CNS tumors. Large head circumference was associated with an increased OR for all histologic subgroups except embryonal CNS tumors. An association with low 5-minute Apgar score was suggested for most histologic subgroups, but most strongly for embryonal CNS tumors (Table 4) and unspecified CNS tumors (Supplementary Appendix). In general, no variation by histologic type was seen with regard to breech presentation.

As children in breech presentation more often have a low Apgar (31) score we wanted to test the association with CNS tumors for these two factors independently. Thus, we repeated the analysis for 5-minute Apgar score excluding children born in breech presentation and the analysis for breech presentation excluding children with a 5-minute Apgar score <7. Both ORs were almost identical with the respective ORs for 5-minute Apgar score and breech presentation of Table 3 (data not shown).

Discussion

This study provides evidence that intrauterine and neonatal factors are associated with a higher risk for a diagnosis of a childhood CNS tumor.

Fetal growth is a highly complex process, which is influenced by both genetic and environmental factors. Low birth weight is not only highly correlated to infant mortality and morbidity but has also been linked to health later in life (32), whereas high birth weight has been associated with an increased overall risk for cancer (17, 18, 33). This includes the findings of a recent meta-analysis (16) of eight studies of a total of 4,162 children with CNS tumors. A birth weight of >4 kg was associated with increased risks for astrocytoma (OR, 1.38; 95% CI, 1.07-1.79) and medulloblastoma (OR, 1.27; 95% CI, 1.02-1.60), but the results were based mainly on small case-control studies that were potentially influenced by recall and selection bias. Our results confirm their findings, however, and add the observation that the increased risk associated with high birth weight is independent of gestational age. Although astrocytoma is the largest histologic subgroup, it is not homogeneous and it includes both low-grade pilocytic astrocytomas and highly malignant glioblastomas. A previous study (9) suggested a stronger association between high birth weight and high-grade astrocytoma than with low-grade astrocytoma. The incidence of CNS tumors in the Nordic countries is higher than in other western countries (4), mainly because of a higher incidence of astrocytic tumors (24). Our observation of a weaker association between high birth weight and astrocytoma than in previous publications might be due to a higher proportion of low-grade tumors in the Nordic study base.

To differentiate between the effects of birth weight per se and intrauterine growth, we calculated the association between birth weight by gestational age and CNS tumors. We observed an increased risk for children who were born LGA, for children of both normal and high birth weight. This is in contrast to the result of the only previous study (20), which was smaller than ours, but maybe more importantly they used a different definition of SGA/LGA than in this study.

The biological mechanisms of the observed associations among high birth weight, increased fetal growth, and an increased risk for CNS tumors are unclear. There are various plausible hypotheses. First, high birth weight is related to larger organ sizes and thus places a larger number of cells at risk for malignant transformation (34). Second, high birth weight, increased growth, and the development of CNS tumors could be indicators of an overall increase in intrauterine cell proliferation, which could be induced by placental or fetal hormones, including growth factors such as insulin-like growth factor (IGF). Circulating levels of IGF-I and IGF-II are highly correlated to fetal growth; the IGF system plays a fundamental role in regulating cell proliferation and differentiation and has antiapoptotic properties (35). Within the CNS, the IGF system is essential for normal neurodevelopment, both in the fetus and in early postnatal life, and IGF receptors are highly expressed at the time of neural tube development (35). Furthermore, overexpression of components of the IGF pathway is observed in medulloblastoma, ependymoma, glioblastoma, and astrocytoma. Several reports have shown that the IGF-I receptor signaling pathway is highly active in medulloblastoma cell lines, animal models, and human tumor tissues (36). Finally, an effect of accelerated growth on carcinogenesis is supported by the increased risk for cancer observed in overgrowth syndromes, such as Beckwith-Wiedemann (37), Soto (38), and acromegaly (39).

A third explanation might be that the intrauterine presence of a CNS tumor could influence the overall growth rate of the fetus through endogenous hormonal mechanisms (36).

In contrast to previous studies (16), we did not observe a linear association with birth weight, but rather a U-shaped relation. The association with low birth weight was due mainly to an association with preterm birth, whereas the higher risk associated with SGA was seen mainly in children born at term (data not shown). Being SGA has not previously been associated with CNS tumors, perhaps because of the small sample sizes in previous studies or differences in the definition of SGA (20). The higher risk we found for preterm birth is in line with a few previous studies (10, 13, 14) but not with those of smaller studies (11, 40-42), studies possibly affected by recall bias (11, 40-42), and the large U.S. study which used a less fine categorization of gestational age (15). It is unclear whether the association between preterm birth and risk for a CNS tumor is restricted to certain histologic subgroups. In our study, the association was strongest for astrocytoma, whereas embryonal CNS tumors has been implicated most often in other studies (10, 13).

The observed association with preterm birth, SGA, and low 5-minute Apgar score might be explained by common biological mechanisms. First, the associations might reflect reverse causality, indicating that these children were born preterm, were SGA, or had a low Apgar score because of a disease that was already present. In

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Table 3. Odds ratios of the association with birth weight, birth weight by gestational age, 5-minute Apgarscore, fetal presentation, and gestational age an childhood CNS tumors stratified by age

CNS overall*	0-14 y			<1 y			0-4 y			5-9 y			10-14 y		
	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)
Birth weight[†]	3,349	15,359		261	1,238		1,329	6,214		1,139	5,206		881	3,939	
<2,500 g	160	617	1.04 (0.84-1.29)	14	48	1.19 (0.58-2.43)	57	254	0.87 (0.62-1.24)	63	212	1.18 (0.83-1.68)	40	151	1.11 (0.73-1.69)
2,500-3,999 g	2,523	11,965	1.00	187	967	1.00	990	4,821	1.00	858	4,009	1.00	675	3,135	1.00
>4,000 g	666	2,777	1.18 (1.07-1.30)	60	223	1.45 (1.03-2.03)	282	1,139	1.27 (1.09-1.47)	218	985	1.06 (0.89-1.26)	166	653	1.21 (1.00-1.47)
Birth weight by gestational age[‡]	3,349	15,359		261	1,238		1,329	6,214		1,139	5,206		881	3,939	
SGA	74	268	1.28 (0.98-1.66)	7	13	2.62 (1.03-6.70)	24	93	1.22 (0.77-1.90)	29	90	1.49 (0.97-2.30)	21	85	1.13 (0.70-1.86)
AGA	3,154	14,646	1.00	237	1,177	1.00	1,259	5,921	1.00	1,067	4,969	1.00	828	3,745	1.00
LGA	121	445	1.26 (1.02-1.55)	17	48	1.74 (0.97-3.10)	46	200	1.08 (0.78-1.51)	43	147	1.35 (0.95-1.92)	32	98	1.46 (0.97-2.19)
Head circumference[§]	2,052	9,068		157	700		817	3,648		698	3,082		537	2,338	
<33 cm[‡]	141	594	1.11 (0.87-1.41)	12	42	1.55 (0.67-3.58)	48	233	0.94 (0.63-1.40)	52	193	1.17 (0.77-1.76)	41	168	1.28 (0.82-2.00)
33 cm	224	978	1.11 (0.93-1.34)	12	63	0.94 (0.44-2.01)	91	384	1.14 (0.86-1.53)	62	317	0.91 (0.65-1.26)	71	277	1.34 (0.95-1.88)
34 cm	431	1,944	1.08 (0.94-1.26)	29	163	0.91 (0.53-1.57)	163	766	1.05 (0.83-1.32)	148	673	1.06 (0.82-1.36)	120	505	1.19 (0.89-1.58)
35 cm	486	2,358	1.00	36	174	1.00	193	952	1.00	167	813	1.00	126	593	1.00
36 cm	447	1,904	1.14 (0.98-1.31)	37	148	1.18 (0.70-2.01)	179	772	1.16 (0.92-1.46)	154	627	1.22 (0.95-1.56)	114	505	1.01 (0.76-1.34)
37 cm	210	914	1.11 (0.92-1.34)	14	79	0.83 (0.41-1.68)	89	383	1.19 (0.89-1.59)	72	322	1.10 (0.79-1.52)	49	209	1.01 (0.68-1.48)
38 cm	79	289	1.28 (0.97-1.70)	7	26	1.25 (0.47-3.29)	35	120	1.51 (0.99-2.31)	29	104	1.33 (0.83-2.15)	15	65	0.90 (0.48-1.67)
>38 cm	34	87	1.80 (1.18-2.74)	10	5	7.52 (2.37-23.93)	19	38	2.40 (1.33-4.31)	1	4	33 2.09 (1.07-4.10)	1	16	0.27 (0.03-2.04)
Gestational age[‖]	3,349	15,359		261	1,238		1,329	6,214		1,139	5,206		881	3,939	
<37	204	832	1.19 (1.00-1.43)	21	70	1.83 (1.05-3.21)	89	348	1.33 (1.01-1.75)	77	294	1.22 (0.90-1.65)	38	190	0.95 (0.64-1.40)
37-40	2,248	10,390	1.00	171	828	1.00	901	4,280	1.00	749	3,453	1.00	598	2,657	1.00
>40	897	4,137	0.98 (0.90-1.07)	69	340	0.90 (0.65-1.24)	339	1,586	0.97 (0.84-1.12)	313	1,459	0.98 (0.85-1.14)	245	1,092	0.98 (0.82-1.16)

(*Continued on the following page*)

Table 3. Odds ratios of the association with birth weight, birth weight by gestational age, 5-minute Apgarscore, fetal presentation, and gestational age an childhood CNS tumors stratified by age (Cont'd)

CNS overall*	0-14 y			<1 y			0-4 y			5-9 y			10-14 y		
	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)
Trend per week[¶]			1.27 (0.99-1.64)												
Trend per week adjusted**			1.58 (1.04-2.44)												
5-min Apgar[††]	2,683	11,834		198	918		1,056	4,815		948	4,168		679	2,851	
≥7	2,647	11,731	1.00	192	906	1.00	1,038	4,774	1.00	935	4,134	1.00	674	2,823	1.00
<7	36	104	1.44 (0.98-2.12)	6	12	2.37 (0.87-6.45)	18	41	1.99 (1.13-3.50)	13	34	1.36 (0.70-2.64)	5	28	0.73 (0.28-1.91)
Fetal presentation[‡‡]	1,947	8,804		180	841		811	3,755		659	2,959		477	2,090	
Other presentation	1,853	8,483	1.00	170	805	1.00	777	3,619	1.00	616	2,843	1.00	460	2,021	1.00
Breech	94	321	1.33 (1.04-1.69)	10	36	1.47 (0.68-3.17)	34	136	1.16 (0.78-1.73)	43	116	1.67 (1.15-2.42)	17	69	1.11 (0.64-1.92)

NOTE: Birth weight was available for > 99%, gestational age for >97%, head circumference for 95%, Apgar at 5 min for 93.5%, and fetal presentation for 99% of the cases and controls in the periods when data were recorded.

*Tumors classified according to the International Classification of Childhood Cancer version 3, main group III, are included.

[†]Conditional ORs and 95% CI adjusted for matching factors of country, sex, age (year and month), and gestational age in completed weeks.

[‡]SGA: <2 SD of the mean birth weight by gestational age of the Nordic population; LGA: >2 SD of the mean birth weight by gestational age of the Nordic population. AGA, appropriate for gestational age. Conditional ORs adjusted for matching factors of country, sex, and year and month of birth.

[§]Head circumference in cm. Conditional ORs adjusted for matching factors of country, sex, and age (year and month), and in addition for gestational age and birth weight.

[‖]Gestational age in completed weeks. Conditional ORs adjusted for matching factors of country, sex, and age (year and month), and in addition for birth weight.

[¶]Trend of gestational age in completed weeks. Conditional OR adjusted for matching factors of country, sex, and age (year and month). Only children born preterm (<37 wk) are included in the analysis.

**Trend of gestational age in completed weeks. Conditional OR adjusted for matching factors of country, sex, and age (year and month), and in addition for birth weight. Only children born preterm (<37 wk) are included in the analysis.

[††]5-min Apgar score. Conditional ORs adjusted for matching factors of country, sex, and age (year and month), and in addition for birth weight.

[‡‡]Fetal presentation independent of mode of delivery. Categorized as breech presentation opposed to other mode of presentation. Conditional ORs adjusted for matching factors of country, sex, and age (year and month), and in addition for birth weight and gestational age.

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Table 4. Association with CNS tumors and birth weight by gestational age, gestational age, head circumference, Apgar score and Fetal presentation stratified by histology

	Ependymoma*			Astrocytoma*			Embryonal CNS tumors*		
	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)
Birth weight by GA[†]	344	1,592		1,419	6,532		614	2,829	
SGA	7	24	1.38 (0.59-3.23)	16	116	0.62 (0.36-1.05)	20	43	2.20 (1.27-3.81)
AGA	322	1,523	1.00 (referent)	1,362	6,225	1.00 (referent)	567	2,703	1.00 (referent)
LGA	15	45	1.59 (0.87-2.91)	41	191	0.95 (0.67-1.34)	27	83	1.58 (1.01-2.47)
Head circumference[‡]	224	994		884	3,920		385	1,725	
<33 cm	18	50	1.70 (0.82-3.54)	62	259	1.06 (0.74-1.52)	27	111	1.38 (0.80-2.39)
33 cm	31	129	1.17 (0.69-1.97)	90	429	0.99 (0.75-1.32)	45	165	1.47 (0.97-2.22)
34 cm	47	202	1.16 (0.73-1.84)	187	871	1.05 (0.84-1.30)	76	357	1.11 (0.79-1.56)
35 cm	49	243		209	1,027		91	460	
36 cm	42	231	0.89 (0.57-1.41)	204	809	1.26 (1.02-1.57)	82	362	1.06 (0.76-1.48)
37 cm	24	107	1.11 (0.63-1.94)	92	382	1.23 (0.92-1.64)	41	185	1.01 (0.66-1.55)
38 cm	9	25	1.79 (0.73-4.36)	28	118	1.20 (0.76-1.91)	17	61	1.22 (0.66-2.24)
>38 cm	4	7	2.47 (0.68-8.97)	12	25	2.40 (1.17-4.93)	6	24	1.10 (0.43-2.86)
5-min Apgar score[§]	276	1,273		1,111	5,010		502	2,299	
≥7	275	1,262	1.00 (referent)	1,100	4,965	1.00 (referent)	504	2,285	1.00 (referent)
<7	1	11	0.35 (0.04-2.77)	11	45	1.04 (0.53-2.03)	10	14	2.75 (1.20-6.31)
Fetal presentation[‖]	189	856		806	3,671		350	1,592	
Other presentation	181	826	1.00 (referent)	773	3,553	1.00 (referent)	334	1,524	1.00 (referent)
Breech	8	30	1.27 (0.55-2.92)	33	118	1.28 (0.86-1.90)	16	68	1.01 (0.57-1.79)
Gestational age									
Trend per week[¶]						1.52 (0.72-3.19)			1.07 (0.79-1.44)
Trend per week adjusted**						4.13 (0.80-21.41)			1.74 (0.83-3.67)

NOTE: Results for the remaining subgroups according to the International Classification of Childhood Cancer version 3. Other glioma, other specified CNS tumors, and unspecified CNS tumors are available in Supplementary Appendix.

*Classified according to the International Classification of Childhood Cancer version 3.

[†] SGA: <2 SD of the expected birth weight by gestational age of the Nordic population, LGA: >2 SD of the expected birth weight by gestational age of the Nordic population. AGA, appropriate for gestational age. OR and 95% adjusted for matching factors of country, sex, and age (year and month).

[‡] Head circumference at birth in cm. Conditional OR adjusted for matching factors of country, sex, and age(year and month), and in addition for birth weight and gestational age.

[§] 5-min Apgar score. Conditional OR adjusted for matching factors of country, sex, and age (year and month), and in addition for birth weight and gestational age.

[‖] Fetal presentation independent of mode of delivery. Categorized as breech presentation opposed to other mode of presentation. Conditional OR adjusted for matching factors of country, sex, and age (year and month), and in addition for birth weight and gestational age.

[¶] Trend of Gestational age in completed weeks. Conditional OR adjusted for matching factors of country, sex, and age (year and month). Only children born preterm (<37 wk) are included in the analysis.

**Trend of gestational age in completed weeks, Conditional OR adjusted for matching factors of country, sex, and age (year and month), and in addition for birth weight. Only children born preterm (<37 wk) are included in the analysis.

support of this hypothesis is the suggestion of a stronger association of being SGA for a diagnosis of CNS tumor in the first year of life and for a low Apgar score and preterm birth in children ages 0 to 4 years; however, the increased risk for CNS tumor of preterm infants was suggested for all age groups <10 years of age, indicating that the latency before diagnosis may be very long. Alternatively, the increased risk of these children for CNS tumors might reflect their vulnerability and the fact that they were more likely to have received more intensive neonatal care. This includes exposure to potentially cytotoxic agents that may pass the immature blood-brain barrier, which is further impaired in cases of neonatal asphyxia (43), as well as diagnostic X-rays, which is frequently used for these babies. An increased cancer risk has been associated with diagnostic X-rays (3), but the link with CNS tumors is still inconclusive. In a relatively small Danish nested case-control study, exposure to diagnostic X-rays could not explain the increased risk for CNS tumors among preterm infants (13).

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Other biological mechanisms may be associated with a low Apgar score. The observation of an increased risk for CNS tumors might reflect a larger number of genetic mutations or greater resistance to apoptosis induced by hypoxia (44). Although there is controversy about the validity of the Apgar score (45), associations between a low 5-minute score and mortality and neurologic outcome have been found in numerous population-based studies (46). It is unclear whether breech presentation is a marker of neurologic impairment that affects fetal movements. This hypothesis is supported by the finding of a slightly increased risk for cerebral palsy and epilepsy among children born breech at term, independent of the mode of delivery (sectio or delivery by vaginal breech), in a large cohort study (31). A CNS tumor could be an example of neurological impairment, in line with our observation (OR, 1.33; 95% CI, 1.04-1.69, for breech opposed to other presentations). One other small study found (7) an association between breech presentation and subsequent diagnosis of a CNS tumor, whereas no association was found in a large international study based on retrospectively collected questionnaires (11). Delivery by vaginal breech is often accompanied by use of instrumentation that may result in head trauma, which has been suggested to be associated with increased risk of CNS tumors, but not confirmed by others (47). This is less likely, however, to explain our finding as most children in breech presentation are born by sectio (31).

Further support for the hypothesis of an *in utero* origin of CNS tumors is the observed association with large head circumference, which was seen for most histologic subgroups. Head circumference reflects the size of the brain but is also increased by greater intracranial pressure before closing of the cranial sutures. Our study confirms the result of a previous Norwegian cohort study (22), with which our data partly overlap. The strongest associations were suggested with a diagnosis in the first few years of life, possibly reflecting increased intracranial pressure; however, a statistically significantly increased risk was observed for all age groups <10 years. The age dependency of the association favors the presence of disease at birth rather than increased head circumference as a risk factor.

The design and size of our study give high credibility to the results. The Nordic national health registries contain mandatory, continuously updated information on vital status, emigration status, cancer, and birth characteristics, and all patients have equal, free access to health care. Thus, use of these virtually complete population registries makes the probability of selection bias negligible. Prospective recording of information on birth ensures that any exposure misclassification will be nondifferential and more likely to result in an underestimate of any association.

Misclassification of CNS tumors in children is always a major concern, owing to the large interobserver variation in pathologic evaluation (48). Furthermore, the many different classifications available in the literature are not always comparable (1, 26). Accordingly, we concluded that it was important to present the estimates of CNS tumors overall in addition to the histology-specific estimates. The risk for misclassification was further minimized by retrieving information on tumor cases from the national cancer registries, the childhood cancer registries, and cross-validated diagnostic data. Information on other risk factors, such as genetic syndromes known to predispose to the development of CNS tumors, was not available; however, these syndromes are rare and in general not associated with preterm birth, fetal growth, or neonatal stress. Knowledge about maternal smoking, assisted reproductive treatment, maternal diabetes and the subsequent risk of CNS tumor (49) in the child is limited, but are known to affect fetal growth (50) and the risk of preterm birth (51, 52) and might have confounded our results.

In conclusion, this Nordic population-based study offers several indications that CNS tumors have a perinatal origin and adds to the increasing scientific evidence of an association between increased growth and cancer. Importantly, however, only a small proportion of CNS tumors can be attributed to the factors identified in our study. The potential links with neonatal exposure require further exploration, as their confirmation will not only increase our understanding of the etiology of these childhood tumors but may ultimately lead to preventive measures.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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