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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Birth Size Characteristics and Risk of Brain Tumors in Early Adulthood: Results from a Swedish Cohort Study

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Abstract

Background: Despite extensive research on the effect of birth size characteristics on childhood brain tumors, very few studies have evaluated the effect of birth size characteristics on the risk of adult brain tumor, and they have provided inconsistent results.

Methods: All individuals born in Sweden between 1973 and 1995 who were still alive and cancer free at their 15th birthday were included in the study ($n = 2{,}032{,}727$). At the end of the study period (December 31, 2010), the study participants were 15 to 37 years old. Incident cases of primary brain tumors were identified through the Swedish Cancer Register.

Results: No association was observed between any birth size characteristics and glioma, although an indication of increased glioma risk associated with high birth weight, or being large for gestational age at birth, was found among men [relative risk (RR) = 1.36, 95% confidence interval (CI), 0.97–1.90; RR = 1.44, 95% CI, 0.99–2.09, respectively]. An increased risk of meningioma was observed among individuals born with a large head circumference (RR = 1.76, 95% CI, 1.01–3.05). Large head circumference was also associated with an elevated risk of neuroma (RR = 1.86, 95% CI, 0.94–3.68). Being born small for gestational age was also related to a higher risk of neuroma (RR = 2.50, 95% CI, 1.31–4.78).

Conclusion: Selected birth size characteristics were associated with increased risk of some brain tumor subtypes in young adults.

Impact: We have presented additional evidence suggesting that birth size characteristics are associated with subsequent primary brain tumor risk in young adults. *Cancer Epidemiol Biomarkers Prev; 25(4); 678–85. ©2016 AACR.*

Introduction

The effect of birth size characteristics, such as birth weight, fetal growth, gestational age, and head circumference, on brain tumor risk has mainly been investigated among children (1–8). Although previous studies have shown that children born with a high birth weight had an elevated risk of brain tumors (1–4), others have found no association (5–8). Moreover, it has been reported that children born with a large head circumference had a higher risk of brain tumors (4, 9, 10), particularly in the first year of life (4, 10). A potential explanation for these associations is that insulin-like growth factor 1 (IGF-1) is positively correlated with both birth weight and head circumference and may also stimulate the proliferation of malignant cells (11). If growth factors are involved in the process of brain tumor onconogenesis, it is, however, plausible that birth weight by gestational age is a more appropriate indicator of risk, as it has been shown for acute lymphoblastic leukemia (6). Therefore, studies have often reported results for both birth weight and birth weight by gestational age (4, 6, 10, 12).

Regarding adult cancers, some studies have suggested that increasing birth weight may increase the risk of certain cancers, particularly breast cancer (13–17). Although two previous studies of brain tumors in adults found no association with birth weight (13, 14), a recent Danish cohort study reported an increased risk of adult glioma associated with increasing birth weight (18).

The aim of this study was to evaluate the association between birth size characteristics (birth weight, head circumference, and birth length) and glioma, meningioma, and neuroma in a cohort of young adults. Gliomas are tumors of the neuroepithelial tissue, with glioblastoma as the most common histologic subtype (19). Gliomas are often malignant with a poor prognosis, they are more common among men, and the incidence increases with age. Meningiomas are generally slow-growing benign tumors that arise from the meninges and are more common among women and in older ages. Intracranial neuromas are most frequently vestibular schwannoma (also called acoustic neuromas), a rare tumor that arises from the Schwann cells of the eighth cranial nerve (20, 21). These are slow-growing benign tumors which may be present for many years before being diagnosed. They are about as common in men as women, and have a peak incidence around 65 years of age. The etiology of schwannoma, meningioma, and glioma is largely unknown. Ionizing radiation increases the risk of meningiomas and gliomas, while bilateral vestibular schwannomas are the hallmark of neurofibromatosis type-2 (22–24). Growth factor receptors and IGF-1 signaling are relevant for tumor growth of all three tumors, but only schwannomas and meningiomas are slowly growing while gliomas can be expected to be

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diagnosed rapidly after tumor initiation (25–28). Due to the fact that previous studies have reported that height was positively associated with adult glioma risk and with cancer risk at other sites (18, 29, 30), adult body size will be taken into consideration in our analyses.

Materials and Methods

The Swedish Medical Birth Register (MBR) was established in 1973 and contains information regarding birth and perinatal characteristics for approximately 98% of the births that have occurred in Sweden (31). All individuals born between 1973 and 1995 who were registered in the MBR were included in the study (n = 2,181,719). They were followed from their 15th birthday until the first of the following events: glioma, meningioma, or neuroma diagnosis, other cancer diagnosis, death, emigration, or end of follow-up (December 31, 2010). At the end of the study period, the study participants were 15 to 37 years old.

Information regarding brain tumor diagnosis, or other cancer diagnosis, was obtained through a record linkage to the nationwide Swedish Cancer Register by means of the unique personal identification number. Glioma, meningioma, and neuroma cases were identified using the International Classification of Disease (ICD) coding: glioma [ICD-7: 193.0 and WHO/HS/CANC/24.1 (C24/hist): 475, 476, 485, 486; ICD-10: C71 and morphology code: 9380-9384, 9390-9394, 9400-9401, 9410-9411, 9420-9424, 9430, 9440-9443, 9450-9451, 9460, 9480-9481, 9505], meningioma (ICD-7: 193.1-193.9 and c24/hist code 461,466; ICD-10: C70 and morphology code 9530-9539), and neuroma (ICD-7: 193.0 and c24/hist code 451, 456; ICD-10: C72.4, C72.5, C72.9 and morphology code 95600 or 95603). In the Swedish Cancer Register, all brain tumors are coded as malignant; therefore, the codes used to identify meningioma and neuroma cases also include benign tumors.

The MBR was used to obtain information about perinatal characteristics, such as birth weight, gestational age, head circumference, birth length, and maternal age. Information regarding paternal age was obtained from the Multigeneration Register. Birth weight by gestational age was used to identify individuals who were born small for gestational age (SGA), appropriate for gestational age (AGA), or large for gestational age (LGA). Individuals were classified as born SGA if they had a birth weight below the 10th percentile of the birth weight distribution, whereas being born LGA was defined as a birth weight above the 90th percentile. These percentiles were estimated for every combination of gestational age, sex, and birth cohort (1973–1980, 1981–1990, and 1991–1995). Individuals who had been diagnosed with cancer before their 15th birthday, i.e., childhood cancer cases, were removed from the study. Moreover, individuals with birth defects (ICD-9: 740-759; ICD-10: Q00-Q99; n = 93,138) or extreme values for certain birth size characteristics were excluded from the study: birth weight <500 g or >6,000 g (n = 120), head circumference <20 cm or >45 cm (n = 43,927), birth length <40 cm or >62 cm (n = 20,618), gestational age <23 weeks or >44 weeks (n = 7,928). After all these exclusions, the study population comprised more than two million individuals (n = 2,032,727).

Information regarding adult height and weight was obtained from the MBR (for women with deliveries) and the Swedish Military Service Conscription Register (for men and women who attended to the military service physical examination). However, this information was available only for a subset of the study population (n = 889,511, 43.8% of the total study population). Information regarding parental socioeconomic index (SEI) at birth was obtained from the national census and was categorized as 0 = low, 1 = medium, 2 = high, or 3 = missing.

The relative risk (RR) of brain tumor associated with birth size characteristics was estimated through calculation of HRs and their 95% confidence intervals (CI) using the Cox proportional hazard model. In this study, the exposures of interest were birth weight (categorized as low birth weight = 500–2,499, normal birth weight = 2,500–3,999, and high birth weight = 4,000–6,000 g), birth weight by gestational age (SGA/AGA/LGA), head circumference (categorized as 20–32 cm, 33–34 cm, 35–36 cm, 37–45 cm), and birth length (categorized as 40–49 cm, 50–52 cm, 53–62 cm). Analyses were adjusted for maternal and paternal age (<25, 25–29, 30–34, 35+), maternal birthplace (Nordic/non Nordic), sex, birth cohort, and parental SEI at birth. At first, the effect of birth size characteristics on the risk of brain tumor subtypes was evaluated in separate models. Subsequently, these characteristics were included simultaneously in the regression models, and analyses were also stratified by sex. The method proposed by Altman and colleagues was used to compare the RRs obtained in stratified analyses (32). To determine whether the effects were mediated by adult body size, the analyses were also adjusted for adult height and weight in the subset of subjects with available information. Cox regression models were fitted using Stata software version 13.1, and P values $\leq$0.05 were considered statistically significant. The proportional hazards assumption was evaluated by regressing the scaled Schoenfeld's residual against survival time (33). No evidence of departure from the proportionality assumption was observed.

Results

Over 500 cases of glioma (n = 555) were identified in the study population between 1988 and 2010, whereas meningiomas (n = 119) and neuromas (n = 84) were less common (Table 1). Seventeen percent of the study participants were born with a high birth weight (≥4,000 g), whereas only 3.4% had a low birth weight (<2,500 g). Even though 10% of the study participants were born SGA, 18% of neuroma cases were born SGA. The study population comprised more men than women (51% vs. 49%); however, almost 60% of the cases of meningioma were women.

No association was found between birth size characteristics and glioma (Table 2). An increased risk of meningioma was found among those who were born with a large head circumference (RR = 1.90, 95% CI, 1.12–3.21) or were between 53 and 62 cm long at birth (RR = 1.79, 95% CI, 1.13–2.84). When the effect of head circumference on meningioma was further adjusted for birth weight by gestational age and length, the risk of meningioma remained approximately the same (RR = 1.76, 95% CI, 1.01–3.05). Similarly, the association between meningioma and length at birth adjusted for birth weight by gestational age and head circumference was essentially the same but only of borderline statistical significance (RR = 1.58, 95% CI, 0.95–2.63). Regarding neuroma, a statistically significant association between being born SGA and neuroma was found in the adjusted analysis (RR = 2.01, 95% CI, 1.14–3.54). After additional adjustment for head circumference and birth length, the association became even stronger (RR = 2.50, 95% CI, 1.31–4.78). A suggestion of an

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Table 1. Frequency of glioma, meningioma, and neuroma according to birth and perinatal characteristics

	N (%)	Glioma	Meningioma	Neuroma
Total	2,032,727	555	119	84
Birth weight (g)				
500–2,499	68,876 (3.4)	20 (3.6)	3 (2.5)	3 (3.6)
2,500–3,999	1,609,686 (79.2)	432 (77.8)	94 (79.0)	67 (79.8)
4,000–6,000	354,165 (17.4)	103 (18.6)	22 (18.5)	14 (16.7)
Gestational age (weeks)				
22–36	95,878 (4.7)	20 (3.6)	3 (2.5)	3 (3.6)
37–41	1,751,746 (86.2)	477 (85.9)	99 (83.2)	74 (88.1)
42–45	185,103 (9.1)	58 (10.4)	17 (14.3)	7 (8.3)
Birth weight by gestational age				
SGA	201,290 (9.9)	53 (9.5)	8 (6.7)	15 (17.9)
AGA	1,625,756 (80.0)	440 (79.3)	95 (79.8)	59 (70.2)
LGA	205,681 (10.1)	62 (11.2)	16 (13.4)	10 (11.9)
Head circumference (cm)				
20–32	169,415 (8.3)	48 (8.6)	6 (5.0)	4 (4.8)
33–34	753,488 (37.1)	207 (37.3)	44 (37.0)	36 (42.9)
35–36	894,183 (44.0)	240 (43.2)	49 (41.2)	31 (36.9)
37–45	215,641 (10.6)	60 (10.8)	20 (16.8)	13 (15.5)
Birth length (cm)				
40–49	640,024 (31.5)	167 (30.1)	37 (31.1)	24 (28.6)
50–52	1,067,258 (52.5)	291 (52.4)	54 (45.4)	48 (57.1)
53–62	325,445 (16.0)	97 (17.5)	28 (23.5)	12 (14.3)
Sex				
Men	1,039,068 (51.1)	304 (54.8)	49 (41.2)	47 (55.9)
Women	993,659 (48.9)	251 (45.2)	70 (58.8)	37 (44.1)
Maternal age				
<25	525,845 (25.9)	150 (27.0)	39 (32.8)	27 (32.1)
25–29	764,782 (37.6)	223 (40.2)	41 (34.4)	38 (45.2)
30–34	513,781 (25.3)	139 (25.1)	23 (19.3)	16 (19.1)
35+	228,319 (11.2)	43 (7.7)	16 (13.4)	3 (3.6)
Paternal age				
<25	243,062 (12.0)	67 (12.1)	14 (11.8)	13 (15.5)
25–29	664,783 (32.7)	193 (34.8)	39 (32.8)	35 (41.7)
30–34	633,664 (31.2)	181 (32.6)	37 (31.1)	21 (25.0)
35+	481,963 (23.7)	111 (20.0)	29 (24.4)	15 (17.9)
Missing	9,255 (0.5)	3 (0.5)	0	0
Maternal birthplace				
Nordic	1,906,626 (93.8)	534 (96.2)	112 (94.1)	82 (97.6)
Non-Nordic	125,842 (6.2)	21 (3.8)	7 (5.9)	2 (2.4)
Missing	259 (0.0)	0	0	0
Parental socioeconomic index at birth				
Low	396,927 (19.5)	110 (19.8)	29 (24.4)	14 (16.7)
Medium	571,390 (28.1)	134 (24.1)	37 (31.1)	26 (30.9)
High	435,428 (21.4)	90 (16.2)	18 (15.1)	14 (16.7)
Missing	628,982 (30.9)	2,221 (39.8)	35 (29.4)	30 (35.7)

increased risk of neuroma was found among those born with a large head circumference (RR = 1.86, 95% CI, 0.94–3.68).

A borderline statistically significant increased risk of glioma was observed among men born LGA (RR = 1.44, 95% CI, 0.99–2.09), but not among women (Table 3). The RR for men born LGA was statistically significantly higher than the RR for women born LGA ($P = 0.04$). The increased risks of meningioma and neuroma associated with a large head circumference were also confined to men (RR = 2.48, 95% CI, 1.22–5.08 for meningioma; RR = 2.51, 95% CI, 1.13–5.59 for neuroma), although these RRs were not statistically significantly different from the ones observed among women ($P = 0.14$ and $P = 0.22$, respectively). An increased risk of neuroma was observed among both men and women born SGA, although it was not statistically significant among women (RR = 2.60, 95% CI, 1.11–6.10 among men; RR = 2.33, 95% CI, 0.85–6.40 among women).

The effect of high birth weight on the risk of brain tumor subtypes (Table 4) was similar to those found for LGA (Table 3). While there was no overall effect, an indication of increased risk of glioma was found for men born with a high birth weight (RR = 1.36, 95% CI, 0.97–1.90 for glioma): this RR was borderline statistically significantly higher than the one observed for women born with a high birth weight ($P = 0.07$).

Adjusting for adult height and weight had little or no effect on the risk estimates (being born LGA and glioma RR = 1.15, 95% CI, 0.72–1.65; large head circumference and meningioma RR = 2.51, 95% CI, 1.30–4.86; large head circumference and neuroma RR = 1.83, 95% CI, 0.81–4.11; being born SGA and neuroma RR = 2.17, 95% CI, 0.99–4.75). No evidence of multiplicative interaction between birth characteristics and adult body size was found (data not shown). Results from sensitivity analyses in which individuals were enrolled at their 20th birthday instead of their 15th birthday, in order to remove the cases of adolescent brain tumor, were in line with the findings observed in the main analysis (data not shown).

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Table 2. RRs of adult brain tumor subtypes associated with birth weight by gestational age, birth length, and head circumference

	Cases	Crude RR	Adjusted RR[a]	Adjusted RR[b]
Glioma				
Birth weight by gestational age				
SGA	53	0.95 (0.71–1.26)	0.94 (0.71–1.26)	0.93 (0.68–1.26)
AGA	440	1 (ref.)	1 (ref.)	1 (ref.)
LGA	62	1.10 (0.85–1.44)	1.11 (0.85–1.45)	1.11 (0.82–1.49)
Head circumference (cm)				
20–32	48	1.01 (0.74–1.37)	1.02 (0.74–1.39)	1.05 (0.75–1.47)
33–34	207	1.00 (0.83–1.20)	1.01 (0.83–1.21)	1.02 (0.84–1.24)
35–36	240	1 (ref.)	1 (ref.)	1 (ref.)
37–45	60	1.07 (0.81–1.41)	1.04 (0.79-1.38)	1.01 (0.75-1.36)
Birth length (cm)				
40–49	167	0.98 (0.81–1.19)	1.00 (0.83–1.21)	1.01 (0.82–1.26)
50–52	291	1 (ref.)	1 (ref.)	1 (ref.)
53–62	97	1.07 (0.85–1.35)	1.05 (0.83–1.32)	1.02 (0.79–1.31)
Meningioma				
Birth weight by gestational age				
SGA	8	0.66 (0.32–1.37)	0.66 (0.32–1.37)	0.71 (0.33–1.52)
AGA	95	1 (ref.)	1 (ref.)	1 (ref.)
LGA	16	1.33 (0.78–2.26)	1.30 (0.76–2.21)	0.92 (0.50–1.68)
Head circumference (cm)				
20–32	6	0.61 (0.26–1.43)	0.56 (0.24–1.32)	0.56 (0.23–1.38)
33–34	44	1.02 (0.68–1.54)	0.96 (0.64–1.45)	0.97 (0.63–1.50)
35–36	49	1 (ref.)	1 (ref.)	1 (ref.)
37–45	20	1.74 (1.03–2.92)	1.90 (1.12–3.21)	1.76 (1.01-3.05)
Birth length (cm)				
40–49	37	1.19 (0.78–1.80)	1.12 (0.74–1.71)	1.36 (0.86–2.15)
50–52	54	1 (ref.)	1 (ref.)	1 (ref.)
53–62	28	1.67 (1.06–2.63)	1.79 (1.13-2.84)	1.58 (0.95-2.63)
Neuroma				
Birth weight by gestational age				
SGA	15	2.02 (1.15–3.56)	2.01 (1.14–3.54)	2.50 (1.31–4.78)
AGA	59	1 (ref.)	1 (ref.)	1 (ref.)
LGA	10	1.34 (0.68–2.61)	1.38 (0.71–2.70)	1.31 (0.62–2.80)
Head circumference (cm)				
20–32	4	0.65 (0.23–1.85)	0.66 (0.23–1.87)	0.53 (0.17–1.59)
33–34	36	1.34 (0.83–2.17)	1.34 (0.83–2.18)	1.23 (0.74–2.04)
35–36	31	1 (ref.)	1 (ref.)	1 (ref.)
37–45	13	1.77 (0.92–3.38)	1.76 (0.92–3.38)	1.86 (0.94–3.68)
Birth length (cm)				
40–49	24	0.86 (0.53–1.41)	0.89 (0.54–1.46)	0.76 (0.43–1.34)
50–52	48	1 (ref.)	1 (ref.)	1 (ref.)
53–62	12	0.81 (0.43–1.52)	0.79 (0.42–1.49)	0.68 (0.33–1.36)

[a]Adjusted for sex, maternal and paternal age, maternal birthplace, birth cohort, and parental socioeconomic index at birth.

[b]Adjusted for sex, maternal and paternal age, maternal birthplace, birth cohort parental socioeconomic index at birth, subject birth weight by gestational age, head circumference, and birth length.

Discussion

This large cohort study, comprising more than two million young adults and more than one thousand cases of adult brain tumor, is the first study that has evaluated the effect of birth size characteristics on adult meningioma and neuroma. An increased risk of neuroma was observed among individuals born SGA. Moreover, individuals born with a large head circumference had a higher risk of meningioma; however, in analysis stratified by sex, this association persisted only among men. There is also a suggestion that men born LGA, or with a high birth weight, had a higher risk glioma.

Very few studies have investigated the association between birth size characteristics and adult brain tumors. A recent Danish cohort study that included 608 glioma cases found a positive association between birth weight and adult glioma risk (18). Similarly to our study, they found that, after stratifying by sex, the positive association was observed only among men. Two previous cohort studies found instead no association between birth weight and adult brain tumors (13, 14). However, these two studies had fewer cases of brain tumor (88 and 333 cases), and the individuals enrolled were older than the ones in our study (respectively 72 to 86 and 28 to 67 years old at the end of the follow-up). It has been suggested that elevated birth weight is an indicator of a larger number of cells in the body, which will then lead to an increased number of cell divisions and therefore to a higher vulnerability to carcinogens (34). Moreover, exposure to high levels of IGF-1 could be involved in brain tumor pathogenesis (28), may lead to a high birth weight, and also stimulate the proliferation of malignant cells (11). However, while growth factors have been suggested as a potential biologic mechanism to explain the positive association between birth weight and breast cancer (17), there is currently no evidence regarding a link between exposure to IGF-1 during gestation and adult glioma risk.

In the current study, we found that individuals born with a large head circumference were at higher risk of both meningioma and

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Table 3. RRs of adult brain tumor subtypes associated with birth weight by gestational age, birth length, and head circumference stratified by sex

		Adjusted RR[a]	
	Cases (men/women)	Men	Women
Glioma			
Birth weight by gestational age			
SGA	28/25	0.84 (0.55–1.29)	1.03 (0.65–1.63)
AGA	238/209	1 (ref.)	1 (ref.)
LGA	42/20	1.44 (0.99–2.09)	0.74 (0.45–1.23)
Head circumference (cm)			
20–32	23/26	1.12 (0.69–1.80)	0.97 (0.60–1.58)
33–34	93/117	0.94 (0.71–1.24)	1.08 (0.82–1.43)
35-36	145/97	1 (ref.)	1 (ref.)
37-45	47/14	0.99 (0.70–1.40)	1.00 (0.56–1.85)
Birth length (cm)			
40–49	83/86	1.26 (0.93–1.71)	0.81 (0.60–1.78)
50–52	152/142	1 (ref.)	1 (ref.)
53-62	73/26	1.04 (0.76–1.42)	0.97 (0.61–1.52)
Meningioma			
Birth weight by gestational age			
SGA	2/6	0.55 (0.12–2.47)	0.79 (0.32–1.95)
AGA	40/58	1 (ref.)	1 (ref.)
LGA	7/9	0.85 (0.35–2.08)	1.02 (0.45–2.31)
Head circumference (cm)			
20–32	0/6	.	0.66 (0.26–1.69)
33–34	15/30	1.27 (0.63–2.57)	0.84 (0.49–1.45)
35–36	19/32	1 (ref.)	1 (ref.)
37–45	15/5	2.48 (1.22–5.08)	1.00 (0.37–2.68)
Birth length (cm)			
40–49	8/30	1.01 (0.43–2.36)	1.58 (0.90–2.77)
50–52	25/31	1 (ref.)	1 (ref.)
53–62	16/12	1.29 (0.65–2.57)	1.89 (0.90–3.96)
Neuroma			
Birth weight by gestational age			
SGA	9/6	2.60 (1.11–6.10)	2.33 (0.85–6.40)
AGA	33/26	1 (ref.)	1 (ref.)
LGA	5/5	1.15 (0.40–3.27)	1.57 (0.53–4.64)
Head circumference (cm)			
20–32	1/3	0.29 (0.04–2.27)	0.75 (0.19–2.92)
33–34	18/18	1.27 (0.63–2.57)	1.18 (0.56–2.49)
35–36	17/14	1 (ref.)	1 (ref.)
37–45	11/2	2.51 (1.13–5.59)	0.85 (0.18–3.91)
Birth length (cm)			
40–49	12/12	0.88 (0.40–1.94)	0.66 (0.29–1.50)
50–52	27/21	1 (ref.)	1 (ref.)
53–62	8/4	0.60 (0.25–1.45)	0.85 (0.27–2.73)

[a]Adjusted for sex, maternal and paternal age, maternal birthplace, birth cohort, parental socioeconomic index at birth, subject birth weight by gestational age, head circumference, and birth length.

neuroma. Previous studies reported that children born with a large head circumference had an increased risk of childhood brain tumors (4, 9, 10), but the effect of head circumference at birth on the risk of adult brain tumor has never been investigated. Similarly to the association between high birth weight and glioma, also in this case, IGF-1 may explain the association between meningioma and large head circumference at birth. In fact, a large head circumference can be caused by *in utero* exposure to high levels of IGF-1. In addition, IGF-1 receptors have been detected in a majority of sporadic meningiomas and IGFBP expressions that vary according to meningiomas aggressiveness (35). However, IGF-1 is not implicated in the occurrence of neuromas. Another explanation for the higher risk of meningioma and neuroma observed among individuals born with a large head circumference is that some of them may have had a congenital brain tumor that caused a tumor-associated hydrocephalus. However, it is unlikely that congenital brain tumors could explain this association because congenital meningiomas and neuromas are very rare, and it is very unlikely that these congenital brain tumors have been diagnosed only more than 15 years after birth (36, 37).

In analyses stratified by sex, we found that certain birth size characteristics were more positively associated with brain tumors in men; only the association between being born SGA and neuroma was also observed among women. A potential explanation for the lack of a positive association among women could be that the effect of birth size characteristics on brain tumor in women may be masked by exposure to estrogens during puberty. It has been suggested that estrogen and sex steroid hormones could play a role in the occurrence of brain tumors, particularly gliomas and meningiomas (38, 39). In fact, gliomas are more common among men, whereas meningiomas occur more frequently in women; moreover, the difference in incidence between men and women starts in childhood and adolescence and increases with age (39). However, when we compared the RRs found in stratified analysis, only the RR observed for men born LGA was statistically significantly higher than the one found for women born LGA. Moreover, even

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Table 4. RRs of adult brain tumor subtypes associated with birth weight

	Cases (men/women)	Crude RR	Adjusted RR[a]	Adjusted RR[b]	Sex	
					Men[c]	Women[c]
Glioma						
Birth weight (g)						
500–2,499	20 (9/11)	1.07 (0.68–1.67)	1.27 (0.77–2.10)	1.24 (0.73–2.12)	0.95 (0.43–2.07)	1.59 (0.77–3.32)
2,500–3,999	432 (220/212)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
4,000–6,000	103 (75/28)	1.12 (0.91–1.39)	1.11 (0.89–1.38)	1.12 (0.86–1.47)	1.36 (0.97–1.90)	0.81 (0.51–1.28)
Meningioma						
Birth weight (g)						
500–2,499	3 (0/3)	0.74 (0.23–2.34)	0.92 (0.26–3.18)	1.15 (0.31–4.26)	.	1.26 (0.31–5.06)
2,500–3,999	94 (37/57)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
4,000–6,000	22 (12/10)	1.13 (0.71–1.79)	1.14 (0.71–1.82)	0.71 (0.40–1.28)	0.62 (0.28–1.40)	0.83 (0.36–1.91)
Neuroma						
Birth weight (g)						
500–2,499	3 (1/2)	1.04 (0.33–3.31)	1.21 (0.33–4.38)	1.72 (0.44–6.73)	1.82 (0.23–14.73)	1.46 (0.23–9.14)
2,500–3,999	67 (36/31)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
4,000–6,000	14 (10/4)	0.99 (0.56–1.78)	1.02 (0.57–1.83)	0.99 (0.49–2.01)	1.18 (0.49–2.84)	0.75 (0.22–2.54)

[a]Adjusted for gestational age, sex, maternal and paternal age, maternal birthplace, birth cohort, and parental socioeconomic index at birth.
[b]Adjusted for gestational age, head circumference, birth length, sex, maternal and paternal age, maternal birthplace, birth cohort, and parental socioeconomic index at birth.
[c]Adjusted for gestational age, head circumference, birth length, maternal and paternal age, maternal birthplace, birth cohort, and parental socioeconomic index at birth.

though men born with a large head circumference had a higher RR of meningiomas and neuromas than women born with a large head circumference, there were no statistically significantly differences between the RRs.

We also found that individuals born SGA had a two times higher risk of neuroma, in both men and women. We are not able to offer an explanation for this finding. However, one case of neuroma born SGA had a diagnosis of neurofibromatosis, whereas other three cases of neuroma that were SGA at birth had recorded diagnosis that could be related to neurofibromatosis; therefore, we speculate that the association between SGA and neuroma may be partly explained by neurofibromatosis.

One of the main strengths of this cohort study is that we had reliable information regarding the birth size characteristics of more than two million Swedish men and women. Moreover, using information from other national registers, we were able to adjust the analyses for potential confounding variables, such as maternal and paternal age, maternal birthplace, sex, and parental SEI at birth. Another advantage of this study was that we were able to adjust for adult height and weight, in order to estimate whether the effect of birth size characteristics was mediated by adult body size. This was important because a previous study reported positive associations between birth weight and several types of cancer, but after adjusting for height, the associations were diluted or no more statistically significant (30). However, adjusting the analyses in the present study for adult body size had no effect on the associations. One limitation of the analyses adjusted for adult body size is that this information was available for less than 50% of the study population, and this subset included individuals that were, on average, healthier and older than the whole study population as it comprised women who gave birth and men and women who attended to the military service physical examination: attendance to this examination was more common among individuals born in the 1970s rather than among those born in later years. Moreover, no information about adult body size is available for men born between 1993 and 1995, as they were underage at the end of the study period. Therefore, by restricting the final analyses only to these individuals, we may have introduced some selection bias, and for this reason, results from the analyses adjusted for adult body size should be interpreted with caution.

One limitation of this study is that, although our cohort included more than two million young adults, there were few cases of meningioma and neuroma. Therefore, we may have had low statistical power to detect associations between birth size characteristics and meningioma or neuroma risk. Moreover, some of the statistically significant associations that we reported are based on a small number of cases. For example, only 15 cases of neuroma were born SGA and only 20 cases of meningioma were born with a large head circumference: for this reason, some of the associations reported in the current study could simply be chance findings. The low number of cases of meningioma and neuroma could also explain the inconsistent findings of the sex-stratified analyses. Moreover, we were not able to investigate the effect of birth size characteristics on the risk of brain tumors among elderly individuals, as only individuals aged 15 to 37 were included in the study. With increasing age, brain tumors become, relatively, more frequent. Therefore, it is possible that including older individuals, or extending the follow-up of the current study, would have led to a dilution of the risk estimates, as it is unlikely that birth size characteristics have an effect on the occurrence of brain tumor at older ages.

Another limitation of the current study is that we did not adjust for factors that are related with birth size and are also potentially related with cancer occurrence, such as maternal diabetes and smoking during pregnancy (40). However, maternal diabetes was very rare in the study population. Less than 11,000 children in the cohort were born from mothers who had diabetes during pregnancy, and only one case of glioma and one case of meningioma were born from mothers with diabetes: therefore, adjusting for maternal diabetes would not have affected the results. Moreover, smoking during pregnancy is available in MBR only from 1983: therefore, adjusting for this variable would have excluded all individuals born between 1973 and 1982.

In conclusion, in this large cohort study of young adults, we found that certain birth size characteristics may increase the risk of some adult brain tumor subtypes. Taking into account adult body

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size had no effect on the associations. However, further studies are needed to confirm our findings and to identify the biologic mechanisms behind these associations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: G. Tettamanti, T. Mathiesen, M. Feychting
Development of methodology: M. Feychting
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Feychting
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Tettamanti, R. Ljung, T. Mathiesen, M. Feychting
Writing, review, and/or revision of the manuscript: G. Tettamanti, R. Ljung, T. Mathiesen, J. Schwartzbaum, M. Feychting
Study supervision: M. Feychting

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