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Birth characteristics and childhood malignant central nervous system tumors: the ESCALE study (French Society for Childhood Cancer).

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► To cite this version:

Nathalie Mallol-Mesnard, Florence Menegaux, Brigitte Lacour, Olivier Hartmann, Didier Frappaz, et al.. Birth characteristics and childhood malignant central nervous system tumors: the ESCALE study (French Society for Childhood Cancer).. *Cancer Detection and Prevention*, 2008, 32 (1), pp.79-86. 10.1016/j.cdp.2008.02.003 . inserm-00273538

HAL Id: inserm-00273538

<https://inserm.hal.science/inserm-00273538v1>

Submitted on 15 Apr 2008

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1 **Birth characteristics and childhood malignant central nervous system** 2 **tumours: the ESCALE study (SFCE*)**

3
4 **Short title:** Childhood CNS tumours and birth characteristics.

5 **Category:** original article

6 **Condensed abstract:** Pre- and perinatal characteristics (birth weight, gestational age, birth order,
7 breastfeeding, congenital anomalies, use of assisted reproductive technology, and foetal losses)
8 were obtained for 209 cases of childhood malignant central nervous system tumour and 1681
9 frequency matched controls. The results suggest an association with a maternal history of
10 miscarriages.

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32 **Sources of support:** This work was supported by grants from INSERM, the Fondation de
33 France, the Association pour la Recherche contre le Cancer (ARC), the Agence Française de
34 Sécurité Sanitaire des Produits de Santé (AFSSAPS), the Agence Française de Sécurité Sanitaire
35 de l'Environnement et du Travail (AFSSET) and the association, Cent pour Sang la Vie.

37 **Liste of abbreviations**

38

39 ESCALE: Etude Sur les Cancers et les Leucémies de l'Enfant (Study on childhood cancers and
40 leukemia)

41

42 EUROCAT: European Surveillance of Congenital Anomalies

43

44 ICCC: International Classification on Childhdod Cancer

45

46 ICD-I-3: International Classification of Diseases for Oncolgy, Third Edition

47

48 RNHE: Registre National des Hémopathies malignes de l'Enfant (National Registry of Childhood
49 Haematological Cancers)

50

51 RNTSE: Registre National des Tumeurs Solides de l'Enfant (National Registry of Childhood Solid
52 Tumours)

53

54 SFCE: Société Française de lutte contre les Cancers de l'Enfant et de l'adolescent (French society for
55 childhood cancer)

56

Abstract

Background: Determining the role of pre- and perinatal factors in the aetiology of childhood malignant central nervous (CNS) tumours, using data from the French national case-control study, ESCALE. **Methods:** ESCALE included all children in France less than 15 years old with a diagnosis of acute leukaemia, lymphoma, malignant CNS tumour, or neuroblastoma (2003-2004). In all, 209 malignant CNS tumour cases (80% of the eligible cases) and 1681 population-based controls (71%) were included using quotas ensuring frequency matching with the cases by age and gender. Case and control mothers were interviewed using a standardised telephone interview, which elicited birth characteristics, congenital malformation, maternal reproductive history, and use of assisted reproductive technologies for the index child. **Results:** The cases and controls did not differ in terms of gestational age at birth, birth weight, birth order, breastfeeding, or parental age at birth. There was no association between assisted reproduction for the index child and malignant CNS tumour (OR = 1.1 [0.6-2.2]). A positive association between a maternal history of one miscarriage and malignant CNS tumour was observed (OR = 1.4 [1.0-2.0], $p < 0.05$), especially for glial cell tumours (other glioma: OR = 2.0 [1.1-3.6]). **Conclusion:** The results suggest a possible association between a maternal history of one miscarriage and the risk of malignant CNS tumour.

Keywords: Epidemiology ; risk factors ; childhood CNS tumour ; birth characteristics

Introduction

Central Nervous System [CNS] tumours are the most common childhood cancer, after leukaemia, in developed countries [1], accounting for 20 to 25% of all childhood neoplasms. In France, about 200 new cases of malignant CNS tumours are diagnosed each year [2]. Most of the cases emerge before the age of 5 years, suggesting that antenatal, perinatal, or early postnatal exposures may be considered potential risk factors [3]. Most of the central nervous system's development occurs during foetal life and over the first 2 or 3 years of extrauterine life, with a trend toward heterogeneity of the various types of central nervous system cells. It is therefore important to consider the period of exposure as well as the type of exposure suspected. Apart from ionizing radiation and a few rare genetic syndromes, the aetiology of childhood CNS tumours is largely unknown. Maternal reproductive history, such as foetal losses and assisted reproduction technologies for the index child, has often been studied, but associations with CNS tumors have rarely been observed. Birth characteristics, such as gestational age, birth weight, parent's age at birth, birth order and congenital malformations, have also been studied. Only congenital malformations seem to be frequently associated with CNS tumors [4, 5]. This paper reports the results for maternal reproductive history, birth characteristics, and the risk of childhood malignant CNS tumors, based on data from the ESCALE study.

Materials and methods

ESCALE is a French national population-based case-control study conducted in 2003 and 2004, which addressed 4 childhood neoplastic diseases (leukaemia, lymphoma, neuroblastoma, and malignant central nervous system tumour) and infectious, environmental, and genetic risk factors. This paper concerns the cases of malignant central nervous system tumours.

Study population and data collection

The design of the study has already been published elsewhere [6]. The cases were all children (0-14 years) whose malignant central nervous system tumour was diagnosed between 2003 and 2004. The cases were living in France at the time of diagnosis. All the cases were recruited directly by investigators assigned to each French paediatric oncology hospital

107 department with the support of the two National Registries of childhood cancer: the National
108 Registry of Childhood Haematological Cancers (RNHE) [7] and the National Registry of
109 Childhood Solid Tumours (RNTSE) [8]. The diagnoses were confirmed by crosschecking with
110 the RNTSE, which was also able to give a histological confirmation for 81% of the cases and a
111 clinical/radiological confirmation for 16%. All the cases have been classified into 4 groups using
112 the third version of the International Classification of Childhood Cancer (ICCC) based on the
113 ICD-O-3 [9]: embryonal tumours (ICD-O-3 codes 9470/3, 9471/3, 9473/3, 9474/3, 9480/3,
114 9508/3), astrocytomas (codes 9380/3, 9400/3, 9401/3, 941/3, 9420/3, 9424/3, 9440/3), other
115 gliomas (codes 9380/3, 9381/3, 9382/3, 9430/3, 9450/3, 9451/3), and ependymomas (codes
116 9390/3-9393/3).

117 For ethical reasons, children who had died or who were receiving palliative care before
118 the inclusion date were not eligible. The cases that were adopted, whose mothers were not
119 French-speaking or who had serious psychiatric disorder were not eligible. Out of the 343 cases
120 of malignant central nervous system tumours (with a /3 behaviour ICD-O-3 codes) diagnosed in
121 France from January 1, 2003, to December 31, 2004, 82 were therefore not eligible (57 early
122 deaths, 1 child receiving palliative care, 14 non-French speaking mothers, 5 non-biological
123 mothers, and 5 psychiatric disorders). Out of the 261 eligible cases, 19 refused to participate and
124 33 could not be contacted by interviewers despite repeated attempts. Finally, 209 (80%) of the
125 eligible cases of malignant CNS tumour were included in the study.

126 The control group was selected from the French population by sampling from 60,000
127 representative addresses taken from the French national telephone directory plus unlisted phone
128 numbers generated randomly. Age and gender quotas were applied to ensure the same age and
129 sex distribution as the group of cases. Additional quotas for the number of children living in the
130 household, based on the last population census, were used to improve the comparability of the
131 controls with the French population with regard to birth order. The latter is related to a number of
132 variables of interest, such as early day-care or breast-feeding, and might otherwise have been
133 biased by sampling. Out of the 50,217 phone numbers contacted, 46,994 were ineligible numbers
134 (22,584 business or inactive numbers, 18,456 households without children, 5,277 outside of the
135 quotas, and 677 with no living, French-speaking biological mother). The eligibility of 862 phone
136 numbers whose owners hung up too early could not be determined. Out of the 2361 remaining

137 eligible controls, 679 parents refused and 1 child had a prior history of neuroblastoma. Finally,
138 1681 controls (71%) were included in the study.

139 The case and control mothers' interviews were conducted by telephone by trained
140 interviewers using the same standardised questionnaire. The interview elicited data on
141 demographic and socio-economic characteristics, parental occupational history, childhood
142 environment, familial and personal medical history, and history of pregnancy. The mother's
143 obstetric history was specifically described: foetal losses (spontaneous, voluntary, or therapeutic)
144 and assisted reproduction for the index child. The mothers were also asked to describe the
145 characteristics of the index child at birth: gestational age, birth weight, parents' age at birth, birth
146 order, breastfeeding, and presence and site of congenital malformations. Malformations were
147 classified as major or minor malformations using the European Surveillance of Congenital
148 Anomalies (EUROCAT) classification [10].

149 *Statistical analysis*

150 The SAS[®] software package (version 9, Cary, North Carolina) was used for all the
151 analyses. Analyses were carried out for all central nervous system tumours considered malignant,
152 in combination and separately for each large group of malignant CNS tumours: ependymomas,
153 embryonal tumours, astrocytomas, and other gliomas. All the variables were treated as
154 categorical variables. Odds ratios (OR) and their 95% confidence intervals (95% CI) were
155 estimated using unconditional logistic regression, closely adjusted for age and gender.
156 Polytomous logistic regression adjusted for age and gender was also used to study the large
157 groups of CNS tumours simultaneously. Additional adjustments for potential confounding
158 factors and mutual adjustments were also made.

159

160 **Results**

161 For the 209 cases, the diagnoses were as follows: ependymoma in 33 cases; embryonal
162 tumours in 100 cases; high grade astrocytoma in 26 cases; other glioma in 45 cases; and other
163 types of CNS tumour in 5 cases. In 7 cases, type 1 neurofibromatosis (NF1) had been diagnosed.

164 The cases did not differ from the controls with respect to gender (table I). Since age
165 quotas for selection of the controls had been defined to enable comparison with the whole case

166 group, there was a small age discrepancy between the CNS cases and controls, particularly for
167 very young children. There were, however, at least 5 controls for each case in each age group,
168 and the mean ages of the cases and controls were very similar (6.3 vs. 6.0, $p = 0.4$). The cases
169 and controls were also similar with respect to the parents' marital status, educational level and
170 socioeconomic category (table I). The number of children living in the household, made
171 comparable to that in the French population by quotas, differed significantly between cases and
172 controls: single children were more frequent for the controls than for the cases.

173 The cases' mothers reported slightly more frequent history of one miscarriage (OR = 1.4
174 [1.0-2.0], $p < 0.05$), but this association was restricted to some glial cell tumours (other gliomas:
175 OR = 2.0 [1.1-3.6]) (table II). When mothers who had also had voluntary or therapeutic abortions
176 were excluded, the results were unchanged. Childhood CNS tumour was not related to voluntary
177 or therapeutic abortion, except for the ependymomas, which were associated with voluntary
178 abortion. There was no association between childhood CNS tumour and assisted reproduction,
179 irrespective of the type of tumour.

180 Overall, gestational age was not associated with CNS tumour, except for embryonal
181 tumours, which were significantly associated with a gestational age at birth of less than 37 weeks
182 (table III). No association between malignant CNS tumours and birth weight or parental age at
183 birth or breast-feeding was observed, irrespective of the type of tumour. An isolated association
184 between birth order and embryonal tumours was observed, with a higher OR for second born
185 children but not for children born subsequently.

186 A total of 8 cases presented with congenital malformations, 6 of which were major
187 malformations (1 cleft lip, 1 cleft palate, 1 congenital malformation of the circulatory system, 1
188 congenital dislocation of the hip, 1 child with webbed toes, and 1 child with spade-like hands)
189 and 2 of which were minor (1 non-neoplastic giant congenital nevus and 1 case of depressions in
190 the skull). No association between major or minor malformations and CNS tumour was
191 evidenced (table III). However, malformations, and especially major malformations, were more
192 often positively, but non-significantly, associated with glial cell tumours (astrocytomas: OR =
193 1.9 [0.2-14], other gliomas: OR = 2.9 [0.9-10]) than with the other types of CNS tumour.

194 The results were unchanged after adjusting for the parents' educational level and
195 socioeconomic category. The results were also unchanged when maternal reproductive history

196 and birth characteristics were included in the same model. Lastly, the exclusion of cases with
197 type 1 neurofibromatosis did not modify the results.

198

199 **Discussion**

200 In short, the present study did not provide evidence of any association between malignant
201 CNS tumours and gestational age at birth, birth weight, birth order, breast-feeding, parental age
202 at birth, or medically assisted reproduction. Glial cell tumours (astrocytoma or other glioma)
203 were significantly associated with a maternal history of miscarriages, and, to a lesser extent and
204 not significantly, with the existence of major congenital malformations.

205 With a statistical power of 80% and an α error of 5%, the study was able to detect odds
206 ratios from 1.5 (30% exposed controls) to 2.2 (5% exposed controls). The statistical power,
207 however, was lower for subtype differences, particularly for uncommon exposures such as
208 malformations.

209 All cases were identified directly by the network of investigators working with the 2
210 French National Registries of Childhood Cancer (RNHE and RNTSE), making selection bias due
211 to the case identification process unlikely. The ineligibility of cases who had died or were under
212 palliative care may have induced a survival bias. To the authors' knowledge, however, none of
213 the variables of interest are known to be survival factors, after accounting for age and tumour
214 type [11]. The study included 19 children who died early, after the interview. They were younger
215 at diagnosis than the children who survived (5.4 vs. 6.1 years old), but comparable, although the
216 numbers were small, with regard to the other characteristics. Therefore, the exclusion of early
217 deaths is unlikely to have induced a major selection bias. The 52 cases (20%) who did not
218 answer the questionnaire had similar age and gender distributions to those of the respondent
219 cases.

220 All the diagnoses were ascertained by the National Childhood Registry of Solid Tumours
221 (RNTSE) and confirmed by histology (81%) and radiology (16%). The results did not change
222 after exclusion of cases whose tumour had not been histologically confirmed.

223 The controls were selected from the general population using the national telephone
224 directory as a random basis together with randomly generated unlisted numbers. The sampling
225 process also made the controls similar to the French population in terms of number of children

226 living in the household and, subsequently, in terms of birth order, when compared with the
227 national perinatal surveys [12, 13]. Comparison with those surveys also showed that the controls
228 were very similar to the French population in terms of paternal age at birth, mother's educational
229 level, voluntary abortion, assisted reproduction, gestational age at birth and birth weight, and
230 maternal reproductive history. The controls' mothers were slightly older than in the overall
231 population. However, no association between the mother's age at birth and childhood CNS
232 tumour was observed and adjusting for that variable did not modify the results. The proportion of
233 congenital malformations in the controls (3.4%) was very close to what was expected on the
234 basis of the Paris Registry of Congenital Malformations (2.2% to 3.2% for children born between
235 1988 and 2000) [14].

236 In order to avoid misclassification with respect to gestational age, birth weight, abortions,
237 and assisted reproduction, only biological mothers were interviewed and identical questionnaires
238 were used for the cases and controls. The frequent examinations and computed tomography and
239 ultrasound scans of children with brain tumours are liable to promote malformation detection and
240 reporting, and may have led to differential misclassification. However, this probably mainly
241 concerns minor, rather than major, malformations and very young children. Major malformations
242 are unlikely to remain undetected after the age of one year. In this study, all the cases with
243 malformations were at least one year old. Because the information on malformations was only
244 given by the mothers, ascertainment may have been incomplete, but similarly, for both the cases
245 and controls.

246 As was the case in this study, the previous studies did not evidence any association
247 between birth order and childhood CNS tumour [15-25]. The association between embryonal
248 tumours and second born children observed in the present study was isolated, with no linear
249 trend with increasing birth order, and would appear to have no particular biological plausibility.

250 A potential link between birth weight and childhood leukemia has been suggested in a
251 meta-analysis of 18 studies [26] and in several studies which were not included in the meta-
252 analysis [27-31]. Insulin-like growth factor has been proposed as a possible explanation [32]. For
253 CNS tumours, no relationship with high birth weight was reported in most of the previous studies
254 [17, 18, 21, 22, 33-37]. The only relationship with high birth weight was reported for
255 astrocytomas [15, 19, 25]. When the results were reported separately for astrocytomas, they were
256 discordant [15, 25].

257 Only 2 of the 10 previous studies [19, 20, 23, 25, 38-42] showed a positive relationship
258 between CNS tumours and premature birth [40, 42]. As in the present study, one of those studies
259 reported a relationship with medulloblastoma [42].

260 Several studies have suggested that breastfeeding may have a protective affect in
261 childhood cancer [43], especially in childhood leukaemia. Nevertheless, none of the studies
262 investigating the role of breastfeeding in childhood CNS tumours, including the present study,
263 observed such inverse association [21, 23, 37, 40].

264 Most studies considering maternal history of foetal losses have not shown any association
265 with CNS tumours [15, 16, 19-21, 23-25]. However, one study investigating malignant CNS
266 tumours also reported a positive association with malignant astrocytoma [15]. A variety of terms
267 were used in the previous studies and it is not always possible to distinguish between
268 spontaneous, voluntary and therapeutic abortions. The terms used by the mothers themselves are
269 probably not always reliable. In the present study, no association was found when all the types of
270 foetal losses (spontaneous, therapeutic, and voluntary abortions) were considered together. The
271 observed association between voluntary abortion and ependymoma remained stable after
272 adjusting for well known confounding factors such as socioeconomic characteristics or smoking
273 during pregnancy. It is therefore difficult to explain except by misclassification of the type of
274 abortion.

275 Many studies have evidenced an association between congenital malformations and CNS
276 tumours [4, 5, 44-46], sometimes with a stronger association when the malformation had a CNS
277 site [44, 46]. In the present study, none of the controls and only one case presented with a brain
278 malformation, and that malformation was minor. Congenital malformations have decreased in
279 France since 1995, thanks to active prevention (folate supplementation) and early screening for
280 major CNS malformations such as spina bifida, enabling therapeutic abortion [14].

281 To the authors' knowledge, only 3 studies on CNS tumour and medically assisted
282 reproduction have been published. None of them reported any association [23, 47, 48]. More
283 generally, no association between childhood malignancies and medically-assisted reproduction
284 has ever been reported [49-52]. The present results are therefore consistent with those of the
285 published studies.

286

Conclusion

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The present study does not support a role of prematurity, birth weight, breastfeeding or parental age in the occurrence of malignant CNS tumours. It suggests that a maternal history of miscarriages may be associated with the risk of malignant CNS tumours.

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Acknowledgements

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We are grateful to: the coordinators of the recruitment of the cases; the staff of the French National Registry of Childhood Solid Tumours, who contributed to case detection and verification; the CSA Institute, who coordinated the selection of the controls and the interviews; the team of interviewers, who interviewed the cases and the controls; and our translator for his skilful revision of the manuscript.

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430

Table I: Characteristics of the cases and controls

	Cases n=209 (%)	Controls n=1681 (%)	Co/Ca^(a) ratio	P
Histological subtypes				
Embryonal tumours	100 (48)			
Ependymomas	33 (16)			
Astrocytomas	26 (12)			
Other gliomas	45 (21)			
Other specified tumors	5 (3)			
Gender				
Male	125 (60)	932 (55)		ns ^(b)
Age at the reference date (years)				
< 2	34 (16)	369 (22)	10.5	0.03 ^(b)
2	15 (7)	153 (9)	10.2	
3	17 (8)	166 (10)	9.8	
4	25 (12)	145 (9)	5.6	
5-6	34 (16)	228 (14)	6.5	
7-8	33 (16)	163 (10)	4.8	
9-11	27 (13)	225 (13)	8.3	
12-14	24 (11)	232 (14)	9.7	
Parent's marital status at interview				
Married	191 (92)	1541 (92)		ns ^(c)
Separated, divorced, widowed	4 (2)	65 (4)		
Single	14 (7)	75 (5)		
Paternal educational level				
≤ High school	126 (60)	1063 (63)		ns ^(c)
> High school	79 (38)	601 (36)		
missing data	4 (2)	17 (1)		
Maternal educational level				
≤ High school	125 (60)	979 (58)		ns ^(c)
> High school	84 (40)	701 (42)		
Socioprofessional categories				
Intellectual and scientific jobs, intermediate profession	92 (44)	713 (42)		ns ^(c)
Administrative employees and sales workers	51 (24)	477 (28)		
Service workers	29 (13)	215 (13)		
Farmers, agricultural, craftsmen and factory workers	37 (18)	274 (16)		

^(a) Co/Ca ratio: Controls/Cases ratio^(b) Chi square test, ns: p>0.05^(c) Non-conditional logistic regression adjusted for age and gender

432 **Table II:** Mother's obstetrical history and childhood central nervous tumours

	Controls n=1681 (%)		All CNS tumours n=209 (%)				Ependymomas (n=33)			Embryonal tumours (n=100)			Astrocytomas (n=26)			Other gliomas (n=45)			
	n	(%)	n	(%)	OR	[IC _{95%}] ⁽¹⁾	n	OR	[IC _{95%}] ⁽²⁾	n	OR	[IC _{95%}] ⁽²⁾	n	OR	[IC _{95%}] ⁽²⁾	n	OR	[IC _{95%}] ⁽²⁾	
All foetal losses																			
No	1031	(61)	115	(55)	1.0	ref	20	1.0	ref	57	1.0	ref	12	1.0	ref	23	1.0	ref	
Yes	650	(39)	94	(45)	1.3	[1.0-1.7]	13	1.1	[0.5-2.2]	43	1.2	[0.8-1.8]	14	1.8	[0.8-4.0]	22	1.5	[0.8-2.6]	
1	403	(24)	58	(28)	1.3	[0.9-1.8]	8	1.1	[0.5-2.5]	26	1.2	[0.7-1.9]	10	2.2	[0.9-5.0]	12	1.3	[0.6-2.7]	
2	247	(15)	36	(17)	1.3	[0.9-1.9]	5	1.1	[0.4-3.0]	17	1.2	[0.7-2.1]	4	1.3	[0.4-4.2]	10	1.7	[0.8-3.6]	
Miscarriages																			
No	1239	(74)	142	(68)	1.0	ref	29	1.0	ref	68	1.0	ref	16	1.0	ref	26	1.0	ref	
Yes	442	(26)	67	(32)	1.3	[1.0-1.8]	4	0.4	[0.1-1.1]	32	1.3	[0.9-2.0]	10	1.7	[0.8-3.8]	19	2.0	[1.1-3.6]	
1	303	(18)	50	(24)	1.4*	[1.0-2.0]	2	0.3	[0.1-1.2]	24	1.4	[0.9-2.3]	10	2.5	[1.1-5.6]	12	1.8	[0.9-3.6]	
≥ 2	138	(8)	17	(8)	1.1	[0.6-1.8]	2	0.6	[0.1-2.6]	8	1.1	[0.5-2.3]	0	-	-	7	2.4	[1.0-5.5]	
Voluntary abortion																			
No	1429	(85)	173	(83)	1.0	ref	23	1.0	ref	85	1.0	ref	21	1.0	ref	39	1.0	ref	
Yes	252	(15)	36	(17)	1.2	[0.8-1.7]	10	2.6	[1.2-5.7]	15	1.0	[0.5-1.7]	5	1.4	[0.5-3.8]	6	0.8	[0.4-2.0]	
1	209	(12)	27	(13)	1.1	[0.7-1.6]	6	1.9	[0.7-4.6]	12	0.9	[0.5-1.8]	4	1.4	[0.5-4.1]	5	0.9	[0.3-2.2]	
≥ 2	43	(3)	9	(4)	1.7	[0.8-3.6]	4	7.2	[2.3- 22]	3	1.1	[0.3-3.7]	1	1.5	[0.2- 12]	1	0.8	[0.1-5.9]	
Therapeutic abortion																			
No	1594	(95)	203	(97)	1.0	ref	33	1.0	ref	97	1.0	ref	24	1.0	ref	44	1.0	ref	
Yes	87	(5)	6	(3)	0.5	[0.2-1.2]	0	-	-	3	0.5	[0.2-1.8]	2	1.4	[0.3-6.2]	1	0.4	[0.1-2.8]	
Assisted reproduction for the index child																			
No	1599	(95)	198	(95)	1.0	ref	29	1.0	ref	97	1.0	ref	25	1.0	ref	43	1.0	ref	
Yes	82	(5)	11	(5)	1.1	[0.6-2.2]	4	2.6	[0.9-7.8]	3	0.6	[0.2-2.1]	1	0.8	[0.1-6.3]	2	0.9	[0.2-3.9]	

433 ⁽¹⁾ Non-conditional logistic regression adjusted on age and gender, ⁽²⁾ Non-conditional polytomic regression adjusted on age and gender

434 * p<0.05

435 **Table III:** Characteristics of children at birth and risk of childhood malignant central nervous tumours

	Controls n=1681 (%)		All CNS tumours n=209 (%)			Ependymomas (n=33)			Embryonal tumours (n=100)			Astrocytomas (n=26)			Other gliomas (n=45)		
	n	(%)	n	(%)	OR [IC _{95%}] ⁽¹⁾	n	OR [IC _{95%}] ⁽²⁾	n	OR [IC _{95%}] ⁽²⁾	n	OR [IC _{95%}] ⁽²⁾	n	OR [IC _{95%}] ⁽²⁾	n	OR [IC _{95%}] ⁽²⁾		
Gestational age																	
< 37 weeks	107	(6)	20	(10)	1.6 [0.8-2.9]	3	1.5 [0.4-6.2]	13	2.5 [1.1-5.4]	1	0.4 [0.1-3.6]	2	0.6 [0.1-3.1]				
37-41 weeks	1515	(91)	177	(87)	1.0 ref	29	1.0 ref	83	1.0 ref	22	1.0 ref	39	1.0 ref				
> 41 weeks	40	(2)	6	(3)	1.4 [0.6-3.3]	1	1.4 [0.2- 11]	1	0.5 [0.1-3.8]	1	1.9 [0.2- 15]	3	2.7 [0.8-9.3]				
Birth weight																	
< 2500	94	(6)	16	(7)	1.0 [0.5-2.5]	2	0.8 [0.1-4.3]	8	0.9 [0.3-2.3]	3	2.2 [0.4- 11]	3	1.7 [0.4-7.1]				
2500-4000	1451	(86)	178	(85)	1.0 ref	29	1.0 ref	83	1.0 ref	23	1.0 ref	38	1.0 ref				
> 4000	135	(8)	15	(7)	1.0 [0.5-1.7]	2	0.8 [0.2-3.3]	9	1.3 [0.6-2.6]	0	-	4	1.2 [0.4-3.5]				
Paternal Age																	
< 25	69	(4)	8	(4)	1.0 [0.4-2.0]	0	-	5	1.3 [0.5-3.3]	2	1.9 [0.4-8.4]	1	0.5 [0.1-3.9]				
25-34	1109	(66)	135	(64)	1.0 ref	22	1.0 ref	63	1.0 ref	17	1.0 ref	30	1.0 ref				
≥ 35	503	(30)	65	(32)	1.1 [0.8-1.5]	11	1.0 [0.5-2.1]	32	1.2 [0.7-1.8]	7	1.0 [0.4-2.4]	14	1.1 [0.6-2.1]				
Maternal Age																	
< 25	163	(10)	17	(8)	0.8 [0.5-1.4]	2	0.7 [0.2-2.9]	7	0.7 [0.3-1.6]	3	1.2 [0.3-4.1]	5	1.1 [0.4-2.9]				
25-34	1235	(73)	158	(76)	1.0 ref	25	1.0 ref	76	1.0 ref	19	1.0 ref	34	1.0 ref				
≥ 35	283	(17)	34	(16)	1.0 [0.6-1.4]	6	1.0 [0.4-2.4]	17	1.0 [0.6-1.8]	4	1.0 [0.3-2.9]	6	0.8 [0.3-2.0]				
Birth order																	
1	708	(42)	80	(39)	1.0 ref	13	1.0 ref	31	1.0 ref	11	1.0 ref	22	1.0 ref				
2	608	(36)	94	(44)	1.3 [0.9-1.8]	15	1.3 [0.6-2.8]	52	1.9 [1.2-2.9]	13	1.3 [0.6-3.0]	14	0.7 [0.4-1.4]				

3 +	365 (22)	35 (17)	0.8 [0.5-1.2]	5 0.7 [0.3-2.0]	17 1.0 [0.6-1.9]	2 0.4 [0.1-1.6]	9 0.8 [0.3-1.7]
Breast feeding⁽³⁾							
Never	775 (49)	93 (45)	1.0 ref	16 1.0 ref	43 1.0 ref	12 1.0 ref	19 1.0 ref
Ever	816 (51)	112 (55)	1.2 [0.9-1.6]	16 0.8 [0.4-1.7]	55 1.3 [0.8-1.9]	13 1.1 [0.5-2.5]	26 1.4 [0.8-2.6]
Breast & Bottle	92 (6)	10 (5)	0.9 [0.5-1.9]	1 0.5 [0.1-3.6]	6 1.3 [0.5-3.1]	2 1.5 [0.3-7.0]	1 0.5 [0.1-3.5]
Breast only	724 (45)	102 (50)	1.2 [0.9-1.6]	15 0.9 [0.4-1.8]	49 1.3 [0.8-2.0]	11 1.1 [0.5-2.5]	25 1.5 [0.8-2.8]
Duration							
≤ 3 months	484 (30)	67 (33)	1.2 [0.5-1.9]	9 0.8 [0.4-1.9]	28 1.1 [0.7-1.8]	10 1.4 [0.6-3.4]	19 1.7 [0.9-3.2]
> 3 months	240 (15)	35 (17)	1.3 [0.8-1.7]	6 1.0 [0.4-2.6]	21 1.7 [1.0-2.9]	1 0.3 [0.1-2.4]	6 1.2 [0.5-3.0]
Congenital malformations							
No	1624 (97)	201 (96)	1.0 ref	32 1.0 ref	97 1.0 ref	25 1.0 ref	42 1.0 ref
Yes	57 (3)	8 (4)	1.1 [0.5-2.3]	1 1.0 [0.1-7.2]	3 0.8 [0.2-2.6]	1 1.2 [0.2-9.2]	3 2.0 [0.6-6.6]
Major	38 (2)	6 (3)	1.2 [0.5-2.9]	0 -	2 0.8 [0.2-3.5]	1 1.9 [0.2-14]	3 2.9 [0.9-10]

436 ⁽¹⁾ Non-conditional logistic regression adjusted on age and gender; ⁽²⁾ Non-conditional polytomic regression adjusted on age and
437 gender; ⁽³⁾ Analysis were performed in children older than 6 months