Environmental Factors and the Risk of Brain Tumours in Young People: A Systematic Review

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Keywords

Brain tumours · Children · Risk factors · Brain cancer · Young adults

Abstract

Background: Brain tumours (BT) are one of the most frequent tumour types in young people, although little is known about their risk factors. **Objective:** The objective of the current work was to review and summarize the scientific literature concerning exposure to environmental factors and BT risk in young people (<25 years old). **Methods:** PUBMED, Embase, Cochrane Library, Scopus, IME-Biomedina (bibliographic database of Consejo Superior de Investigaciones Científicas) and Web of science databases were searched. A score to assess the quality of the methodological information was created. **Results:** Some possible associations between BT risk in young people were reported for cadmium, consumption of well water, presence of nitrate or nitrate-nitrogen in tap water, mother's passive smoking, air pollution, parental handling of pesticides at home and/or profes-

sional pesticide treatment within houses, living on a farm and/or with farm animals, some parental occupations and high amount of meat consumption. **Conclusions:** Although many of the studies reviewed suggest associations between the environmental exposures and BT in children and young adults, at present no reliable conclusion can be drawn as most results are based on small number of cases and exposure assessment is limited. Large-scale studies with better exposure assessment are needed to shed light on these possible associations, especially on exposure to heavy metals, tap water consumption, pesticides and parental smoking.

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Introduction

Brain tumours (BT) are the second most common cancer type in children and young adults. Around 215,000 cancers in children (0–14 years old) are diagnosed in the world every year, and about 85,000 among adolescents and young adults (15–19 years old), according to esti-

mates from the International Agency for Research on Cancer [1]. The incidence rates vary by country from 1.15 to 5.14 cases per 100,000 persons in paediatric populations [2]. The incidence also varies by ethnicity [3].

Little is known about risk factors for BT, with genetic factors and ionising radiation being currently the only well-established risk factors [4]. Migrant studies showed no difference in BT incidence between the offspring of migrants and those of the local population [5], suggesting that environmental exposures might play an important role in BT aetiology [6]. Associations with specific environmental factors, such as heavy metals; pesticides; contaminants in tap/well water or air pollution, have been suggested to play a role in the aetiology of the disease in young people [7–12]. Additionally, other factors affecting children like mother's diet during pregnancy, environmental tobacco smoke or parental occupation have been suggested as potential risk factors for BT in young people, but results are inconsistent [7, 8, 13].

The main objective of this paper was to review and summarize the scientific literature about exposure to environmental factors and BT risk in young people.

Materials and Methods

Several searches were made by 1 reviewer (A.Z.-M.) in the following databases: PUBMED, Embase, Cochrane Library, Scopus, Google Scholar, Web of Science and IME (bibliographic database of Consejo Superior de Investigaciones Científicas). Additional articles were found searching the bibliographic references section of articles found (handpicking). Search terms were grouped using the Boolean operators "OR" and "AND." The advanced searches were population AND exposure AND outcome (detailed searches are at the online suppl. Material; for all online suppl. material, see www.karger.com/doi/10.1159/000500601). The keywords used for population were child* OR adolescen* OR young adult OR infan* OR pediatric OR paediatric. The keywords searched for exposure were heavy metal OR cadmium (Cd) OR lead OR tap water OR nitrate OR nitrite OR disinfection byproduct OR meat OR diet OR pesticide OR farm OR parental occupation* OR air pollution OR toxic* OR tobacco smoke OR smoking cigarette OR pregnancy OR cell phone OR mobile (because the literature on tumour risk from ionising radiation exposures is regularly reviewed by various national and international committees we did not include this exposure in our review). The keywords used regarding outcomes were brain cancer OR brain tumo* OR brain neoplasm OR meningioma OR glioma OR primitive neuroectodermal tumo* OR medulloblastoma OR primitive neuroectodermal tumour (PNET) OR central nervous system tumo*. The asterisk (*) is a wildcard used by the search engines to identify all occurrences that start with the indicated term and are followed by any other letter or letters. For Google scholar we did different searches using a combination of keywords because we could not do the complete search directly (online suppl. material). No restriction for publication year or lan-

Fig. 1. Flowchart of article selection.

guage was applied. The first searches were performed in July 2016 with additional weekly searches in PUBMED until January 2019.

All articles found were entered into a database using Zotero reference manager ($n = 3,037$; Fig. 1). To select the articles related to our topics of interest, we first deleted duplicates ($n = 418$). Then, we excluded the reviews ($n = 258$), meta-analyses ($n = 19$) articles and pooled analysis ($n = 1$), although we checked them whether we had missed any articles. Two thousand three hundred and forty-one titles and abstracts were read to remove articles not meeting our inclusion criteria. We used the following inclusion criteria:

- Studies including young people (<25 years old),
- Studies assessing pre- or post-natal exposure to environmental risk factors,
- Original articles about BT in general or for some specific BT types. Articles that included central nervous system tumours in general, and provided no results for BT, were excluded.

With the removal of 2,230 articles, we read 111 whole papers. Forty-two articles were further excluded because they did not meet our inclusion criteria. One article was added in 2018 after periodical searches, leaving 70 articles for the final analysis. Co-au-

thors independently assessed the studies for inclusion. Discrepancies were resolved by a final discussion of the research group.

To classify the completeness of the methodological information reported in each article, we created a score (online suppl. Table 3) using the 9 main items of methods of the Strengthening the Reporting of Observational Studies in Epidemiology statement [14]. Each sub-item scored as “+” if it was included or “-” if not included. Additionally, the PRISMA checklist was completed (online suppl. Table 4). No review protocol has been published.

We subdivided the results section into 8 parts: heavy metals, tap water consumption, parental cigarette smoking, air pollution (mainly related to vehicle traffic), exposures related to farms (such as pesticide exposure and contact with animals), non-ionising radiation (such as mobile phones and power lines), parental occupation, and diet (especially meat consumption). Each article was analysed by exposure period: preconception, pregnancy or childhood. When feasible, we also analysed exposure of mother, father or postpartum of the child separately. We also stratified by specific type of pollutant, chemical, or specific occupation, or other exposure categories, as available.

For those exposures that were considered sufficiently homogeneous across studies, that is, using similar exposure categories with exposure assessment by comparable methods, we performed DerSimonian-Laird random effect meta-analyses. The random effects model was chosen because the data sources, the age ranges and study designs varied. The I^2 statistic was applied to report heterogeneity from Cochran's Q test. I^2 reflects the proportion of total variance estimated to be attributable to between-study heterogeneity. Studies with I^2 values of <25, 25–50, 50–75 and >75% were defined as no, low, moderate and high heterogeneity, respectively. Forest plots of BT risk estimate for mother's smoking (online suppl. Fig. 1), mother's passive smoking (online suppl. Fig. 2), pesticides (online suppl. Fig. 3), living on a farm (online suppl. Fig. 4) and meat consumption (online suppl. Fig. 5) were performed. Effect estimates are relative risks (OR, HR or incident rate ratio) with 95% CIs. Heterogeneity I^2 and p value are shown in all figures. Tumor type and exposure period are shown in the right columns.

Results

From the 70 articles included in this review, 69% ($n = 49$) had >200 cases recruited. Nevertheless, only 23% ($n = 16$) of the articles exceeded 500 cases. Most studies (50%) were conducted in the United States and Canada, the rest were from different countries all over the world, in particular Australia, and European countries. Table 1 provides descriptive information for each study included, classified by type of epidemiological design, with information on the number of participants, age range and geographic and/or ethnic origin of the population.

Table 2 summarizes the main results of the articles grouped by risk factor, indicating the exposure assessment method, the exposure period and the number of cases and controls included in the analyses.

Heavy Metals

Only one case – control study [11] was available on the association between heavy metals and BT in young people. Based on only 4 BT cases, Sherief et al. [11] reported significantly higher levels of Cd in cases than controls ($p < 0.001$) in all biological samples tested: blood, urine, scalp hair and nails.

Tap Water Consumption

Three case – control studies of the association between water consumption and BT in children and young adults (<20 years old) were found. The first found no increased risk of BT among children whose mothers reported drinking well water (a hole drilled into the earth) exclusively during their pregnancies. Analyses by region, however, showed an increased risk in the Seattle region (OR 2.6 [1.3–5.2]) and a decreased risk in Los Angeles County (OR 0.2 [0.1–0.8]). An inverse association with borderline statistical significance was found with the presence of >10 mg/L of nitrate in the tap water, while an increased BT risk, based only on 13 cases and 3 controls exposed, was found for nitrite levels above 1 mg/L (OR 8.8 [2.1–46]) [15].

A further study by the same group [10], including some of the same regions as in Mueller et al. [15] and others from Europe and Canada, confirmed the findings in the US regions and found an increased risk in Canada. No association was found between BT and nitrates or nitrite concentrations overall though an increased OR was found for nitrite concentration >5 mg/L after excluding bottled water users. Analysis by tumour type showed an increased risk for nitrite (with no indication of a dose – response) only for astroglial tumours.

The third case – control study [16] found an increased risk of malignant BTs, and central nervous system tumour was found for having lived in a municipality with exposures >0.31 mg/L of nitrate-nitrogen (>1.37 mg/L nitrate) in drinking water compared to lower exposures. The study examined the possible interaction with the presence of calcium and magnesium in the water with high levels of nitrate-nitrogen, assuming that the main source of calcium and magnesium exposure was local drinking water, but no significant association was found.

Parental Cigarette Smoking

Twenty-two case – control [7, 17–36] and 2 cohort studies [37, 38] were found examining the association between cigarette smoking. Among the 20 articles that explored maternal active smoking during preconception or pregnancy and BT risk, 2 case-control studies found no association with childhood BT. Ten case – control

Table 1. Descriptive information about each article included

Reference	Age, years	Number cases	Number controls	Geographic/ethnic origin of the population
<i>Case and control studies</i>				
Gold et al. [26], 1979	<20	84	73	Baltimore (US)/white and black
Hemminki et al. [56], 1981	<15	948 (282 BT)	NA	Finland/ethnicity NA
Preston-Martin et al. [25], 1982	0–24	209	209	Los Angeles (US)/white and black
Olshan et al. [62], 1986	0–15	51	142	Washington state (US)/ethnicity NA
Nasca et al. [65], 1998	<15	338	676	NY state (US)/ethnicity NA
Wilkins and Koutras [66], 1988	<20	491	491	Ohio (US)/white
Savitz et al. [52], 1988	0–14	356 (67 BT)	278	US/hispanic, non-hispanic and black
Howe et al. [27], 1989	1–21	74	138	Canada/ethnicity NA
Wilkins and Sinks [61], 1990	<20	110	193	Ohio (US)/white and non-white
John et al. [29], 1991	0–14	223 (48 BT)	196	Colorado (US)/white, black and other
Feingold et al. [55], 1992	0–14	252 (67 BT)	222	US/other white, Spanish surname and black
Kuijten et al. [57], 1992	<15	163	163	US/black and non-black
Bunin et al. [73], 1993	<6	166	166	US and Canada/white and non-white
Gold et al. [30], 1993	<18	361	1,083	US/white, black, Asian and other
Bunin et al. [19], 1994a	<6	321	321	US and Canada/white and non-white
Bunin et al. [72], 1994b	<6	155	155	US and Canada/white and non-white
Cordier et al. [22], 1994	0–15	75	113	France/ethnicity NA
Filippini et al. [18], 1994	1–15	91	321	Northern Italy/ethnicity NA
McCredie et al. [23], 1994a	0–14	82	164	New South Wales/ethnicity NA
McCredie et al. [39], 1994b	0–14	82	164	New South Wales/ethnicity NA
Sarasua and Savitz [75], 1994	0–14	234 (45 BT)	206	US/ethnicity NA
Norman et al. [28], 1996	0–19	540	801	US/white, black, Hispanic, Asian and other
Gurney et al. [51], 1996	<20	195	366	US/white, other
Preston-Martin et al. [47], 1996a	<19	540	801	US/white, Hispanic, African American and other
Preston-Martin et al. [71], 1996b	<19	540	801	US/white, Latino, African American and other
Cordier et al. [54], 1997	<15	251	601	UE/ethnicity NA
Ji et al. [31], 1997	<15	680 (107 BT)	642	Shangai/white, black, Hispanic, native american Indian, Asian, other
Pogoda and Preston-Martin [24], 1997	0–19	224	218	US/non-Hispanic white, Hispanic, African American, Asian and other
Holly et al. [45], 1998	0–20	540	801	US/white, white-Hispanic, black, Asian, American Indian and other
McKean-Cowdin et al. [58], 1998	0–19	540	801	US/white, Latino, African American, Asian and other
Filippini et al. [17], 2000	0–15	244	502	Lombardy (Italy)/ethnicity NA
Hu et al. [32], 2000	0–18	82	246	Heilongjiang (China)/ethnicity NA
Lubin et al. [76], 2000	<18	300	574	Israel/Asian-African, European-American, Israeli
Cordier et al. [53], 2001	<19	1,218	2,223	Australia, UE, Canada, US/ethnicity NA

Table 1. (continued)

Reference	Age, years	Number cases	Number controls	Geographic/ethnic origin of the population
Mueller et al. [15], 2001	<20	540	801	US, Europe, Canada and Australia/white, black, Hispanic, Asian, native American and other
Pogoda and Preston-Martin [70], 2001	<19	540	801	US/white, black, Hispanic, Asian and other
Schüz et al. [42], 2001	<15	466	2,458	Germany/ethnicity NA
Filippini et al. [21], 2002	0–19	1,218	2,223	North America, Europe, Australia/ethnicity NA
Efird et al. [44], 2003	0–19	1,213	2,213	US, Europe, Canada and Australia/ethnicity NA
Van Wijngaarden et al. [63], 2003	0–6	321	321	US and Canada/white and non-white
Cordier et al. [7], 2004	0–19	1,218	2,223	Australia, Canada, US and Europe/ethnicity NA
Mueller et al. [10], 2004	<20	836	1,485	US, Europe, Australia/ethnicity NA
Bunin et al. [74], 2005	<6	315	315	US/non-Hispanic white, non-Hispanic black and other
Pavlovic et al. [33], 2005	0–19	60	60	Serbia/ethnicity NA
Bunin et al. [77], 2006	<6	315	315	US and Canada/white, black, Hispanic and other
Plichart et al. [34], 2008	<15	209	1,681	France/ethnicity NA
Rosso et al. [41], 2008	<6	318	318	US/non-Hispanic white, non-Hispanic black, other
Pogoda et al. [69], 2009	0–19	1,218	2,223	Europe, US, Canada, Australia/Latino, other white, black, and other
Shim et al. [43], 2009	0–10	263	263	Atlantic Coast/white, African American and other
Saito et al. [50], 2010	0–14	55	99	Japan/Asian
Aydin et al. [48], 2011	7–19	352	646	Denmark, Norway, Sweden and Switzerland/ethnicity NA
Weng et al. [16], 2011	0–19	457	457	Taiwan/ethnicity NA
Christensen et al. [46], 2012	7–19	352	646	Denmark, Norway, Sweden and Switzerland/ethnicity NA
Li et al. [49], 2012	<15	394 BT	11,820	Taiwan/ethnicity NA
Milne et al. [20], 2013	0–15	302	941	Australia/European and non-European
Barrington-Trimis et al. [35], 2013	<10	202	286	US/African-American, non-Hispanic white, Hispanic, Asian and other
Greenop et al. [9], 2013	0–14	374	1,467	Australia/European and non-European
Keegan et al. [64], 2013	<15	11,119	11,039	Britain/ethnicity NA
Peters et al. [60], 2013	0–14	306	950	Australia/European and non-European
Greenop et al. [78], 2014	<15	293	726	Australia/European and non-European
Peters et al. [59], 2014	0–14	306	950	Australia/European and non-European
Sherief et al. [11], 2015	3–14	350 (4 BT)	350	Egypt/ethnicity NA
Von Ehrenstein et al. [12], 2015	<6	183	30,569	California/non-Hispanic white, Hispanic of any race and other
Danysh et al. [40], 2016	0–5	315 CNS	1,575	Texas/non-Hispanic white, Hispanic and other
Vienneau et al. [36], 2016	7–19	352	646	US/ethnicity NA

Table 1. (continued)

Reference	Age, years	Number cases	Number controls	Geographic/ethnic origin of the population
<i>Cohort studies</i>				
Kristensen et al. [67], 1996	0–14	323,359 (182 BT)		Norway/ethnicity NA
Brooks et al. [38], 2004	<15	1,441,942 (480 BT)		Sweden/ Nordic and other countries classification
Tettamanti et al. [37], 2016	<23	2,577,305 (1,039 BT)		Sweden/Nordic and other
Spycher et al. [68], 2017	<16	2,129,264 (227 CNST)		Switzerland/ethnicity NA
<i>Ecological study</i>				
Danysh et al. [8], 2015	<15	1,949		Texas/non-Hispanic white, non-Hispanic black, Hispanic and other

BT, brain tumours; CNST, central nervous system tumours; NA, no available.

studies and 2 cohorts studies found indications of increased risk in the offspring, though the increase was only statistically significant in 2 of the case – control studies [17, 18] and in 1 of the cohorts studies (HR 1.24 [1.1–1.53], based on 144 exposed cases) [38]. Additionally, 6 studies found non-statistically significant reduced risks. The overall meta-analytical estimate of the effect of mothers' active smoking is a relative risk of 1.09 (1.00–1.18), with little heterogeneity ($I^2 = 16\%$; online suppl. Fig. 1).

Regarding mothers' passive smoking (including exposed to fathers' smoking) before conception or during pregnancy, 14 studies suggested an increased risk in their offspring, being statistically significant in 7. One article studied the association of the exposure in conjunction with paternal occupational exposure to polycyclic aromatic hydrocarbons with a significant increased risk of BT [7]. Two other studies found non-statistically significant reduced risks of BT [19, 20]. There was a significantly increased meta-analytical effect estimate of 1.32 (1.12–1.55) for mothers' passive smoking but with moderate heterogeneity ($I^2 = 56\%$; online suppl. Fig.2).

When examining direct exposure of the child, 2 articles [21, 39] reported no association between early infancy or childhood passive smoking and BT (one based on a large sample size). Another study [22] found a significantly increased risk of BT for passive smoking exposure during childhood (OR 2.3 [1.1–4.6]; based on 41 cases).

Air Pollution

Two case – control studies were retrieved evaluating the link between air pollution and BT. In the first [12], a significantly increased risk of specific types of BT was

found in relation to some pollutants, including acetaldehyde, butadiene or polycyclic aromatic hydrocarbons measured in outdoor air of the residence of the child during pregnancy or the first year of life. The second [40] found an increased risk of ependymoma and PNET in offspring of mothers who resided at time of birth within 500 m of a major roadway and a significantly increased risk of ependymoma for offspring of mothers who resided in areas with high traffic density at time of birth [40]. In an ecological study [8], researchers found a significantly increased risk of astrocytomas in areas with concentrations of 1,3-butadiene between 0.031 and 0.046 $\mu\text{g}/\text{m}^3$, and of BT in general in areas with diesel particulate matter between 0.218 and 0.784 $\mu\text{g}/\text{m}^3$ compared to areas with lower concentrations ($<0.218 \mu\text{g}/\text{m}^3$). No increased risk was observed, however, in areas with highest diesel particulate matter concentrations ($>1.426 \mu\text{g}/\text{m}^3$).

Pesticides Exposure and Living on a Farm

We found 11 articles studying the relationship between BT in young people and pesticide exposure, and 8 focusing more generally on living on a farm as a surrogate for the many exposures that may be encountered in such settings.

Seven studies [9, 19, 22–25, 41] that assessed exposure to pesticides during pregnancy suggested an increased risk of BT, in particular astrocytoma and high-grade glioma, but not PNET (when subtypes were considered). The increases were statistically significant in 4 of the studies [9, 23, 24, 41], and the highest OR was seen for exposure to pesticides when mothers were professionals (OR 4.5 [1.39–15.14] for high-grade gliomas, in a small group of 6 cases and 116 controls) [9]. The overall meta-

Table 2. Summary of results by exposure

Exposure	Reference	Exposure ass. method	Exposure period	Risk factor	Cases/controls included in the analysis	Results
<i>Case and control studies</i>						
Heavy metals	Sherief et al. [11], 2015	Serum, urine, hair, nails	Childhood	Cd	4/350	Cd concentration in cases is > than controls ($p < 0.001$)
	Mueller et al. [15], 2001	Face-to-face interview	Pregnancy	Well water only	18/16 2/11	OR 2.6 (1.3–5.2) in Seattle OR 0.2 (0.1–0.8) in Los Angeles area
		Water samples of residences	Before pregnancy	Any nitrate measured Any nitrite measured	15/41 13/3	OR 0.6 (0.3–1.1) OR 8.8 (2.1–46)
Water	Mueller et al. [10], 2004	Face-to-face interview	Pregnancy and child's first year of life	Well water only	45/83 and 134/281 304/315	OR 6.1 (1.4–27.0) in Canada and OR 3.0 (1.4–6.2) in Seattle OR 0.1 (0.1–0.9) in Los Angeles area
		Water samples	Pregnancy and child's first year of life	>50 mg/L of nitrate	14/28	OR 1.5 (0.6–3.8) bottled water users excluded
				>5 mg/L of nitrite	6/8	OR 5.2 (1.2–23.3) bottled water users excluded
				1–<5 mg/L of nitrite	151/537	OR 4.3 (1.4–12.6) only for astroglial tumours
				>5+ mg/L of nitrite	151/537	OR 5.7 (1.2–27.2) only for astroglial tumours
				>9.3 mg/L of Mg in drinking water	152/132	OR 1.24 (0.79–1.95) if >0.31 mg/L of nitrate
Cigarette smoking	Weng et al. [16], 2011	Water samples of tap water in residences	Childhood and adolescence	>0.31 mg/L of nitrate-nitrogen >34.8 mg/L of Ca in drinking water	190/229 152/132	OR 1.40 (1.07–1.84) for MBT, CN OR 1.30 (0.84–1.99) if >0.31 mg/L of nitrate
	Gold et al. [26], 1979*	Interview (NA type)	Before pregnancy	Maternal smoking	5 (+/-)/1 (-/+) discordant pairs	OR 5 ($p = 0.22$)
	Preston-Martin et al. [25], 1982*	Telephone interview	Pregnancy	Maternal passive smoking	58 (+/-)/39 (-/+) discordant pairs	OR 1.5 ($p = 0.03$)
	Howe et al. [27], 1989	Face-to-face interview	Pregnancy	Maternal smoking	18/32	OR 1.4 (0.7–3.0)
				Paternal smoking	31/58	OR 1.13 (0.62–2.09)
	John et al. [29], 1991	Face-to-face interview	Year prior to birth	Maternal passive smoking	NA	OR 1.6 (0.7–3.5) from environmental father smoking tobacco
			First trimester of pregnancy	Maternal smoking	NA	OR 0.7 (0.3–1.7)
	Gold et al. [30], 1993	Face-to-face interview	Pregnancy	Paternal smoking >1 year	65/185	OR 1.1 (0.7–1.8) for astrocytic tumours
			During year index was born	Maternal smoking >1 year	64/217	OR 1.0 (0.7–1.4) for astrocytic tumours
	Bunin et al. [19], 1994a*	Telephone interview	Pregnancy	Maternal smoking	60–64/58–63	OR 1.0 (0.6–1.7) for astrocytomas or PNET
				Mother passive smoking	83/83 79/81	OR 0.9 (0.6–1.5) for astrocytomas OR 0.9 (0.8–1.2) for PNET
	Cordier et al. [22], 1994*	Face-to-face interview	Pregnancy	Maternal smoking	19/23	OR 1.6 (0.7–3.5)
			Childhood	Child passive smoking	41/51	OR 2.3 (1.1–4.6)
	Filippini et al. [18], 1994	Face-to-face interview	Pregnancy	Maternal smoking	18/59	OR 1.7 (0.8–3.8)
				Maternal passive smoking	37/92	OR 2.2 (1.1–4.5; >2 h/day exposed)
			Conceptional period	Maternal passive smoking	38/123	OR 1.6 (0.8–3.2)
				Maternal smoking	38/105	OR 1.9 (1.0–3.9)
	McCredie et al. [23], 1994a*	Face-to-face interview	Pregnancy	Maternal passive smoking	41/49	OR 2.2 (1.2–3.8) from environmental paternal tobacco smoke
	McCredie et al. [39], 1994b*	Face-to-face interview	Childhood	Child passive smoking	NA	No association
	Norman et al. [28], 1996	Face-to-face interview	Pregnancy	Maternal smoking	92/152	OR 0.98 (0.72–1.30)
				Maternal passive smoking	207/262	OR 1.2 (0.9–1.6)
				Paternal smoking	174/238	OR 1.2 (0.9–1.5)
	Ji et al. [31], 1997	Face-to-face interview	Before conception	Father smoker and mother non smoker	21/17	OR 2.7 (0.8–9.9) for >5 pack-year

Table 2. (continued)

Exposure	Reference	Exposure ass. method	Exposure period	Risk factor	Cases/controls included in the analysis	Results
	Pogoda and Preston-Martin [24], 1997*	Face-to-face interview	Pregnancy	Maternal smoking	32/29	OR 1.1 (0.6–1.9)
	Filippini et al. [17], 2000	Telephone interview	Before pregnancy	Maternal smoking	110/199	OR 1.2 (0.9–1.7)
				Paternal smoking	155/293	OR 1.2 (0.9–1.7)
			Early pregnancy	Maternal smoking	83/160	OR 1.5 (1.0–2.3)
				Maternal passive smoking (never active smoker)	101/168	OR 1.8 (1.2–2.6)
	Hu et al. [32], 2000	Face-to-face interview	Before pregnancy	Maternal passive smoking	44/124	OR 1.3 (0.8–2.2)
			Pregnancy	Maternal passive smoking	46/129	OR 1.17 (0.67–2.04)
				Maternal smoking	9/18	OR 1.20 (0.45–3.23)
	Filippini et al. [21], 2002	Face-to-face interview	Pregnancy	Maternal smoking	210/422	OR 0.9 (0.8–1.1)
			Mother regular exposure	Maternal passive smoking	706/1,257	OR 1.1 (1.0–1.3) any smoking source
					20/162	OR 1.9 (1.1–3.2) exp. at home for unspecified glial tumour
			Child 1st year life	Child passive smoking	564/1,087	OR 1.0 (0.8–1.1)
	Cordier et al. [7], 2004	Face-to-face interview and job exposure matrix	Pregnancy	Maternal PAH exposure	46/90	OR 1.0 (0.7–1.4) PAH exposure from occupation
					152/305	OR 0.9 (0.7–1.2) PAH exposure from smoking
					13/22	OR 1.2 (0.6–2.5) smoking and occupational exposure
			Preconception	Paternal PAH exposure	484/784	OR 1.3 (1.1–1.6) PAH exposure from occupation
					273/590	OR 1.1 (0.9–1.3) PAH exposure from smoking
					272/646	OR 1.4 (1.1–1.7) smoking and occupational exposure
	Pavlovic et al. [33], 2005*	Face-to-face interview	Pregnancy	Maternal smoking	16/24	OR 0.6 (0.3–1.3)
	Plichart et al. [34], 2008	Telephone interview	Pregnancy	Maternal smoking	6/325	OR 1.3 (0.5–3.2) for astrocytomas
					10/325	OR 1.2 (0.6–2.4) for other gliomas
			Year prior to birth	Paternal smoking	18/746	OR 3.1 (1.3–7.6) for astrocytomas
					17/746	OR 0.8 (0.4–1.4) for other gliomas
	Milne et al. [20], 2013	Mailed and telephone questionnaires	Preconception	Maternal smoking	72/206	OR 0.99 (0.70–1.40)
				Paternal smoking	74/222	OR 0.99 (0.71–1.32)
			Pregnancy	Maternal smoking	51/157	OR 0.89 (0.61–1.31)
				Paternal smoking	71/202	OR 1.04 (0.74–1.46)
	Barrington-Trimis et al. [35], 2013	Face-to-face interview	Pregnancy	Maternal smoking	21/47	OR 0.55 (0.29–1.05)
				Paternal smoking	45/57	OR 1.03 (0.62–1.71)
	Vienneau et al. [36], 2016	Face-to-face interview	Pregnancy	Maternal smoking	90/133	OR 1.23 (0.90–1.68)
Air pollution	Von Ehrenstein et al. [12], 2015	Air toxics info. about participant's residences from the California air resources board	Pregnancy	Acetaldehyde	34/25,361	OR 2.30 (1.44–3.67) for PNET
				1,3-Butadiene	38/27,189	OR 2.23 (1.28–3.88) for PNET
				PAH	27/21,368	OR 1.44 (1.15–1.80) for medulloblastomas
			During first year of life	Ortho-dichlorobenzene	23/18,040	OR 3.27 (1.17–9.14) for PNET
				1,3-Butadiene	31/25,688	OR 3.15 (1.57–6.32) for PNET
				Lead	20/16,680	OR 1.40 (0.97–2.03) for astrocytomas

Table 2. (continued)

Exposure	Reference	Exposure ass. method	Exposure period	Risk factor	Cases/controls included in the analysis	Results
	Danysh et al. [40], 2016	Birth certificate registry about participant's residences	At time of birth	Mother living within 500 m of a major roadway Maternal residential high roadway density	23/1,173 9/1,173 15/591	OR 3.08 (0.91–10.42) for ependymomas OR 3.04 (0.38–24.07) for PNET OR 4.23 (1.20–14.88) for ependymomas
Pesticides	Gold et al. [26], 1979*	Interview (NA type)	Prior to diagnosis	Home use of pesticides	16 (+/-)/7 (-/+) discordant pairs	OR 2.3 ($p = 0.1$)
	Preston-Martin et al. [25], 1982*	Telephone interview	Pregnancy	Often or occasional contact with pesticides Home treated with pesticides	42/29 10/10	OR 1.50 ($p = 0.08$) OR 1.0 ($p = 0.6$)
			Childhood	Often or occasional contact with pesticides Home treated with pesticides	26/24 36/42	OR 1.10 ($p = 0.44$) OR 0.90 ($p = 0.29$)
	Howe et al. [27], 1989	Face-to-face interview	Prior to diagnosis	Pesticides	19/38	OR 0.94 (0.47–1.90)
	Bunin et al. [19], 1994a*	Telephone interview	Pregnancy	Insect sprays or pesticides	34/26 31/39	OR 1.5 (0.8–2.7) for astrocytomas OR 0.7 (0.4–1.4) for PNET
				Home treated with pesticides	24/31 34/33	OR 0.7 (0.4–1.4) for astrocytomas OR 1.0 (0.6–1.9) for PNET
	Cordier et al. [22], 1994*	Face-to-face interview	Pregnancy	House treated with pesticides	18/21	OR 1.8 (0.8–4.1)
			Childhood	House treated with pesticides	31/36	OR 2.0 (1.0–4.1)
	McCredie et al. [23], 1994a*	Face-to-face interview	Pregnancy	House treated with pesticides	20/24	OR 2.0 (1.0–3.9)
	Pogoda and Preston-Martin et al. [24], 1997*	Face-to-face interview	Pregnancy	Flea/tick pesticides	76/57; 29/18 33/17	OR 1.7 (1.1–2.6) all ages; OR 2.5 (1.2–5.5) in children diagnosed 0–4 years OR 2.2 (1.1–4.2) pest. prepared/cleaned by mother
			Childhood	Flea/tick pesticides	106/102	OR 1.0 (0.7–1.4)
	Schüz et al. [42], 2001*	Mailed or telephone interviews	Childhood	Exposed once per year to household pesticides	8/96; 5/96	OR 2.45 (1.09–5.45) for astrocytomas; OR 1.14 (0.44–2.95) for medulloblastomas
				Garden treated with pesticides	16/290; 13/290	OR 0.91 (0.48–1.71) for astrocytomas; OR 0.81 (0.43–1.53) for medulloblastomas
				Exposed to wood preservatives	53/746; 39/746	OR 1.91 (1.22–3.01) for astrocytomas; OR 1.15 (0.74–1.77) for medulloblastomas
	Rosso et al. [41], 2008	Telephone interview	Pregnancy	Father lawn care using insecticides	105/67	OR 1.6 (1.0–2.5) for medulloblastomas or PNET
			After children birth	Father lawn care using insecticides	111/70	OR 1.7 (1.1–2.6) for medulloblastomas or PNET
	Shim et al. [43], 2009	Telephone interview	During 2-year before child's birth and occurrence BT	Parental herbicides use	53/27; 26/24 (discordant pairs)	OR 1.9 (1.2–3.0) for astrocytomas; OR 1.0 (0.6–1.8) for PNET
				Father herbicides use	40/20; 21/18 (discordant pairs)	OR 2.0 (1.2–3.4) for astrocytomas; OR 1.1 (0.5–2.0) for PNET
				Residential herbicide use + paternal occupational exposure	52 (+/-)/26 (-/+); 25 (+/-)/21 (-/+) (discordant pairs)	OR 1.9 (1.2–3.1) for astrocytomas; OR 1.2 (0.6–2.1) for PNET
				Residential herbicide use by father + paternal occupational exposure	41 (+/-)/22 (-/+); 22 (+/-)/18 (-/+) (discordant pairs)	OR 1.8 (1.1–3.1) for astrocytomas; OR 1.0 (0.5–2.0) for PNET
	Greenop et al. [9], 2013	Mailed and telephone interviews	In year before pregnancy Pregnancy	Home or garden treated with pesticides	72/187	OR 1.54 (1.07–2.22)
				Home or garden treated with pesticides	46/116 6/116	OR 1.52 (0.99–2.34) OR 4.58 (1.39–15.14) for high grade gliomas
				Home or garden treated with pesticides	96/303 39/91	OR 1.04 (0.75–1.43) OR 1.63 (1.02–2.60) if child was at home during pest treatment
			After children birth			

Table 2. (continued)

Exposure	Reference	Exposure ass. method	Exposure period	Risk factor	Cases/controls included in the analysis	Results
	Gold et al. [26], 1979*	Interview (NA type)	Early childhood	Living on a farm	12 (+/-)/3 (-/+) discordant pairs	OR 4.0 ($p = 0.04$)
				Sick pets	9 (+/-)/2 (-/+) discordant pairs	OR 4.50 ($p = 0.07$)
Farm and animals	Bunin et al. [19], 1994a*	Telephone interview	Pregnancy	Living on a farm	5/8; 14/6	OR 0.5 (0.1–1.8) for astrocytoma; OR 3.7 (0.8–23.9) for PNET
			Childhood (>1 year)	Living on a farm	6/9; 14/6	OR 0.4 (0.1–1.6) for astrocytomas; OR 5.0 (1.1–46.8) for PNET
	Cordier et al. [22], 1994*	Face-to-face interview	Pregnancy	Living on a farm	8/2	OR 6.7 (1.2–38.0)
				Cat scratches	10/3	OR 5.1 (1.2–21.6)
			Childhood	Living on a farm	4/2	OR 2.5 (0.4–16.1)
	McCredie et al. [23], 1994a*	Face-to-face interview	Pregnancy	Mother live/work on farm	5/11	OR 0.9 (0.3–2.6)
	McCredie et al. [39], 1994b*	Face-to-face interview	Childhood	Lived/worked on farm	4/12	OR 0.6 (0.2–1.9)
				Contact with horses	6/17	OR 0.7 (0.3–1.8)
	Holly et al. [45], 1998	Face-to-face interview	Pregnancy	Lived or worked on a farm	22/21	OR 1.6 (0.9–2.9)
				Exposed to pigs	16/11	OR 3.8 (1.2–12.0)
			Childhood	Lived or worked on a farm	35/36	OR 1.5 (0.9–2.4)
	Efird et al. [44], 2003	Face-to-face interview	Pregnancy	Living on a farm	75/119	OR 1.3 (1.0–1.8)
				Farm animals	63/95	OR 1.4 (1.0–1.9)
			Childhood	Living on a farm	92/164	OR 1.3 (1.0–1.7)
				Living any farm animal	82/144	OR 1.3 (0.9–1.8)
				Living on a farm starting <6 months of age	62/89	OR 1.6 (1.1–2.2)
Non-ionizing radiation	Christensen et al. [46], 2012	Face-to-face or mailed interview	Pregnancy	Living on a farm	352/38	OR 0.40 (0.19–0.88)
			Childhood	Living on a farm	12/43	OR 0.57 (0.28–1.17)
				Contact with birds	84/206	OR 0.7 (0.5–0.9)
			Childhood (3 years exp.)	Goats and sheep	17/57	OR 0.5 (0.3–0.9)
	Savitz et al. [52], 1988	Face-to-face or telephone interview	Childhood	Electrical and magnetic fields	25/204	OR 0.82 (0.23–2.93) for high magnetic fields; OR 0.53 (0.15–1.81) for high electric fields
	Bunin et al. [19], 1994a*	Telephone interview	Pregnancy	Electrically heated waterbed	32/38	OR 0.9 (0.5–1.7) for astrocytomas
					35/34	OR 1.0 (0.6–1.9) for PNET
				Electric blanket	19/18	OR 1.0 (0.5–2.2) for astrocytomas
					21/18	OR 1.2 (0.6–2.5) for PNET
	McCredie et al. [23], 1994b*	Face-to-face interview	Childhood	Electric blanket	6/23	OR 0.4 (0.2–1.2)
				Electrically heated water bed	1/10	OR 0.2 (0–1.5)
	Preston-Martin et al. [47], 1996a	Face-to-face interview	Pregnancy	Electric blanket	53/485	OR 0.9 (0.6–1.2)
				Electrically heated waterbeds	55/484	OR 0.9 (0.6–1.3)
			Childhood	Electric blanket	28/512	OR 1.0 (0.6–1.7)
				Electrically heated waterbeds	22/518	OR 1.2 (0.7–2)
Non-ionizing radiation	Gurney et al. [51], 1996	Mailed and telephone interviews	Childhood	Magnetic fields	23/52	OR 0.9 (0.5–1.5) for high level of magnetic fields
	Schüz et al. [42], 2001*	Mailed or telephone interviews	Pregnancy	Electric blanket	10/111	OR 1.81 (0.85–3.86) for astrocytomas
					1/111	OR 0.51 (0.01–3.83) for ependymomas
					9/111	OR 2.02 (0.95–4.28) for medulloblastomas

Table 2. (continued)

Exposure	Reference	Exposure ass. method	Exposure period	Risk factor	Cases/controls included in the analysis	Results
	Saito et al. [50], 2010	Face-to-face interview and magnetic fields measurements	Childhood	Magnetic fields	3/1	OR 10.90 (1.05–113) for $\geq 0.4 \mu\text{T}$ in the bedroom
	Aydin et al. [48], 2011	Face-to-face interview	Childhood	Regular users of mobile phones Started to use mobile phones 5 years before the diagnosis	194/329 46/81	OR 1.36 (0.92–2.02) OR 1.26 (0.70–2.28)
	Li et al. [49], 2012	From National Communication Council	Child exp. 5 years prior to diagnosis	RF exposure	114/4,923	OR 1.14 (0.83–1.55) for above median annual power density estimated (168.07 WYs/km ²)
Parental oc.	Hemminki et al. [56], 1981	Maternity welfare district information	Pregnancy	Mother factory worker	5 discordant pairs	OR 8 ($p < 0.05$) for cases recruited 1969–1975
				Father machine repair men	14 discordant pairs	OR 4.39 ($p < 0.05$)
				Father painter	14 discordant pairs	OR 2.59 ($p < 0.10$)
					7 discordant pairs	OR 5.0 ($p < 0.05$)
	Olshan et al. [62], 1986	Face-to-face interview	1 year prior to birth to time of diagnosis	Father ever employment in the aerospace industry	8/12	OR 2.10 (0.79–5.60) for children 0–9 years old
					1/16	OR 0.12 (0.01–1.08) for children 10–15 years old
	Nasca et al. [65], 1988	Telephone interview	Postnatal	Father industrial exposure to ionizing radiation	8/676 21/676	OR 2.48 (1.01–5.57) for more exposure OR 2.4 (1.3–4.3) for less exposure
	Wilkins and Koutras [66], 1988	Computerized records of births and deaths	Postnatal	Agriculture, forestry and fishing occupation	NA exp.	OR 2.4 (1.2–4.9)
				Father construction occupation	NA exp.	OR 2.3 (1.3–4.1)
				Father chemicals, drugs and paints occupation	NA exp.	OR 1.9 (0.7–5.1)
				Father metal occupation	NA exp.	OR 1.8 (1.1–2.9)
				Father machinery occupation	NA exp.	OR 1.7 (1.1–2.7)
				Food and tobacco occupation	NA exp.	OR 0.9 (0.5–1.8)
				Medicine and science	79/45	OR 0.6 (0.2–1.5)
				Electrical assembling, installing and repairing occupations	19/9	OR 2.7 (1.2–6.1)
	Wilkins and Sinks [61], 1990	Telephone interview	Pregnancy	Father agriculture occupations	4/491	OR 1.6 (0.4–6.1)
			Preconception	Father metal employment	13/491	OR 3.3 (1.3–8.5)
			Preconception	Father aromatic nitro compounds exposure	NA exp.	OR 5.7 (1.4–23.2) for picric acid exposure
	Feingold et al. [55], 1992	Job-exposure matrix and face to face/telephone interviews	Preconception	Father exp. to any chemical	22/99	OR 0.9 (0.4–2.2)
				Father exp. to hydrocarbons	18/84	OR 0.8 (0.3–2.0)
				Father exp. to inorganic compounds	17/54	OR 1.2 (0.4–3.3)
				Father exp. to lead	2/12	OR 0.7 (0.1–3.8)
				Father exp. to asbestos	10/23	OR 1.7 (0.6–5.3)
				Father exp. to physical agents	14/65	OR 0.9 (0.3–2.3)
	Kuijten et al. [57], 1992	Telephone interview	Pregnancy	Father exp. to transportation industry	2 (+/-)/14 (-/+) discordant pairs	OR 0.1 (0.0–0.6) for astrocytomas
				Father exp. to ionizing radiation	9 (+/-)/8 (-/+) discordant pairs	OR 1.1 (0.4–3.4) for astrocytomas
			Preconception	Father exp. to electromagnetic fields exp.	8 (+/-)/9 (-/+) discordant pairs	OR 0.9 (0.3–2.6) for astrocytomas
				Father exp. to metal-related occup.	21 (+/-)/20 (-/+) discordant pairs	OR 1.1 (0.5–2.1) for astrocytomas
			Postnatal	Father exp. to metal-related occup.	15 (+/-)/18 (-/+) discordant pairs	OR 0.8 (0.4–1.8) for astrocytomas
			Preconception	Father exp. to electrical repairing	8 (+/-)/1 (-/+) discordant pairs	OR 8.0 (1.1–356.1) for astrocytomas
			Postnatal	Father exp. to painting worker	5 (+/-)/2 (-/+) discordant pairs	OR 2.5 (0.4–26.2) for astrocytomas
			Preconception	Nurse (mother)	8 (+/-)/1 (-/+) discordant pairs	OR 8.0 (1.1–356.1) for cases 0–4 years and astrocytomas

Table 2. (continued)

Exposure	Reference	Exposure ass. method	Exposure period	Risk factor	Cases/controls included in the analysis	Results
	Cordier et al. [54], 1997	Face-to-face interview	Five years before birth	Mother exp. to solvents Mother exp. to PAH Father exp. to solvent Father exp. to PAH	251/601	OR 1.3 (0.9–2.0) and OR 2.4 (1.2–4.9) for high exposures OR 0.7 (0.4–1.2) OR 1.0 (0.7–1.5) OR 1.5 (1.1–2.1)
	McKean-Cowdin et al. [58], 1998	Face-to-face interview	Five years before birth	Father chemical-petroleum industry Mother chemical-petroleum industry Father electrical workers Father agriculture-farming Mother agriculture-farming Mother material packager and handler	20/24 13/10 34/23 22/27 5/11 13/14	OR 2.1 (1.1–3.9) for astroglial tumours OR 3.3 (1.4–7.7) for astroglial tumours OR 2.3 (1.3–4.0) OR 1.2 (0.7–2.1) OR 0.93 (0.34–2.60) OR 2.3 (1.1–5.1)
	Cordier et al. [53], 2001	Face-to-face interview	During the last 5 years period before the child's birth Preconception	Father agriculture Mother agriculture occupations Father petroleum activities Father metal products occupations Mother metal products occupations Father aerospace activities Mother aerospace activities Father painting occupations Mother painting occupations Father electrical work occupations Mother electrical work occupations Mother textile activities Mother health services occupation	80/104 22/39 14/10 84/174 7/17 30/59 10/24 31/43 9/9 98/168 22/36 35/54 57/61	OR 1.3 (1.0–1.8) OR 1.1 (0.7–1.9) OR 3.4 (1.4–8.2) for astroglial tumours OR 0.9 (0.7–1.1) OR 0.6 (0.3–1.6) OR 0.8 (0.5–1.3) OR 0.6 (0.3–1.3) OR 1.2 (0.8–2.0) OR 1.7 (0.7–4.5) OR 1.1 (0.9–1.5) OR 1.3 (0.7–2.2) OR 1.7 (1.1–2.7) OR 1.7 (1.1–2.4)
	Van Wijngaarden et al. [63], 2003*	Telephone interview	During work history in general	Mother insecticide exposure Father farm worker	53/35; 37/37 21/19; 28/30	OR 1.9 (1.1–3.3) for astrocytomas; OR 1.0 (0.6–1.7) for PNET OR 1.1 (0.5–2.3) for astrocytomas; OR 0.9 (0.5–1.7) for PNET
	Keegan et al. [64], 2013	NRCT and birth registers	Postnatal	Father occupational solvents exposures Father occupational paints exposures	44/27 74/94	OR 1.71 (0.99–2.93) for ependymoma OR 0.7 (0.5–1.0) for astrocytomas
	Peters et al. [60], 2013	Mailed and telephone interviews	Any time before birth Preconception	Mother occup. exposure to diesel Father occup. exposure to diesel	17/29 53/124	OR 2.03 (1.09–3.81) OR 1.62 (1.12–2.34)
	Peters et al. [59], 2014	Mailed and telephone interviews	Any time before birth Preconception	Mother occup. to chlorinated solvents Father occup. exposure to solvents Father occup. to aromatic solvents	3/4 43/92 NA exp	OR 8.59 (0.79–78.9) OR 1.55 (0.99–2.43) OR 1.76 (1.10–2.82)
	Preston-Martin et al. [25], 1982*	Telephone interview	Pregnancy	Meat consumption	127/140	OR 2.3 ($p = 0.008$) for 2 or more times per week
	Bunin et al. [73], 1993	Telephone interview	Pregnancy	Vegetables Bacon	166/166 166/166	OR 0.37 (0.19–0.72) for PNET in higher quartile OR 1.71 (1.02–2.89) for PNET according mother's weekly consumption

Table 2. (continued)

Exposure	Reference	Exposure ass. method	Exposure period	Risk factor	Cases/controls included in the analysis	Results
Diet	Bunin et al. [72], 1994b	Telephone interview	Pregnancy	Cured meats	41/41	OR 1.7 (0.8–3.4) for astrocytic gliomas in higher quartile
				Vitamin C	35/35	OR 0.7 (0.4–1.5) for astrocytic gliomas in higher quartile
				Iron supplements	NA	OR 0.5 (0.3–0.8) for astrocytic gliomas
				Fruits/juices	34/34	OR 0.7 (0.3–1.4) for astrocytic gliomas in higher quartile
	Cordier et al. [22], 1994*	Face-to-face interview	Pregnancy	Cured meat consum.	63/103	OR 0.7 (0.2–3.0)
	McCredie et al. [23], 1994a*	Face-to-face interview	Pregnancy	Cured meat consum.	29/34	OR 2.5 (1.1–5.7) for high consumption
	Sarasua et al. [75], 1994	Face-to-face interview	Pregnancy	Hot-dogs	33/125	OR 2.3 (1.0–5.4) 1 or more times/week
			Childhood	Hot-dogs	29/93	OR 2.1 (0.7–6.1) 1 or more times/week
	Preston-Martin et al. [71], 1996b	Face-to-face interview	Pregnancy	Cured meat consum.	60/60	OR 2.1 (1.3–3.2) for eating at least twice a day
					47/40	OR 2.2 (1.4–3.6) for eating cured meat and no vitamins were taken
					201/377	OR 0.54 (0.39–0.75) for additional multivitamin consumption during 3 trimesters
	Lubin et al. [76], 2000	Personal interview	Pregnancy	Nitrate	300/574	OR 1.5 (0.8–1.7) for high level of intake
			Childhood	Nitrate	300/574	OR 1.2 (0.8–1.7) for high level of intake
			Pregnancy	Vitamin C	300/574	OR 1.1 (0.7–1.7) for the highest intake
	Pogoda and Preston-Martin [70], 2001	Face-to-face interview	Pregnancy	Cured meat (nitrite exposure)	377/601	OR 1.2 (0.9–1.6) for low concentrations
					27/24	OR 2.3 (1.3–4.4) for 0.50–0.99 mg of nitrite average daily
					6/10	OR 1.3 (0.5–3.3) for higher concentration
	Bunin et al. [74], 2005	Telephone interview	Pregnancy	Fruits/juices	<i>n</i> = 158	OR 0.6 (0.3–1.1) for PNET/medulloblastoma
				Red meat	<i>n</i> = 354	OR 1.1 (0.8–1.7) for more than once per month
				French fries	<i>n</i> = 187	OR 2.4 (1.2–4.9) for more than twice per week
				Non-fresh peaches or similar	<i>n</i> = 97	OR 0.5 (0.3–0.8)
	Bunin et al. [77], 2006	Telephone interview	Periconception	Cured meat and fish	<i>n</i> = 182	OR, 1.4 (0.8–2.2) for 2–3.5 times/week
					<i>n</i> = 152	OR 1.0 (0.6–1.9) for >5 times/week
			Midpregnancy	Cured meat and fish	<i>n</i> = 176	OR 1.1 (0.7–1.9) for 2–3.5 times/week
			Midpregnancy		<i>n</i> = 154	OR 1.0 (0.6–1.8) for >5 times/week
	Pogoda et al. [69], 2009	Face-to-face interview	Pregnancy	Cured meat	284/413; 161/413	OR 1.5 (1.1–2.1) for all BT in higher quartile
					142/2,170;	OR 2.5 (1.1–5.8) for pilocytic astrocytomas;
					96/2,170;	OR 2.1 (1.1–4.3) for anaplastic astrocytomas;
					199/2,170	OR 1.8 (1.2–2.7) for unspecified astrocytomas
					104/2,170	OR 2.0 (0.4–2.9) for ependymomas
				Cruciferous vegetables	96/2,184	OR 0.4 (0.3–0.7) for astrocytomas
				Grains	292/526	OR 0.9 (0.8–0.9) for all BT in higher quartile
					122/2,171	OR 0.3 (0.1–0.6) for malignant gliomas
				Fresh fish	237/566	OR 0.7 (0.6–0.9) for all BT in higher quartile
				Fresh fish	122/2,182	OR 0.5 (0.3–0.6) for malignant gliomas
				Fresh fish	96/2,182	OR 1.6 (1.1–2.4) for anaplastic astrocytomas
				Non-cured meat	199/2,183	OR 1.2 (1.1–1.3) for unspecified astrocytomas
	Greenop et al. [78], 2014	Mailed questionnaire	Pregnancy	Coffee	150/359	OR 1.23 (0.92–1.64)
				Tea	189/493	OR 1.0 (0.7–1.4)

Table 2. (continued)

Exposure	Reference	Exposure ass. method	Exposure period	Risk factor	Exposed cases	Results
<i>Cohort studies</i>						
Cigarette smoking	Brooks et al. [38], 2004	Face-to-face interview	Pregnancy	Maternal smoking	144	HR 1.24 (1.01–1.53)
	Tettamanti et al. [37], 2016	Face-to-face interview	Pregnancy	Maternal smoking	147 87	RR 1.11 (0.92–1.33) for 1–9 cigs/day RR 1.15 (0.91–1.44) for 10+ cigs/day
Parental oc.	Kristensen et al. [67], 1996	Information by national agricultural censuses	NA	Parental pesticide purchase	41	RR 1.71 (1.11–2.63) for BT aged 0–14
					22	RR 3.37 (1.63–6.94) for non-astrocytic neuroepithelial tumours aged 0–14
	Spycher et al. [68], 2017	Census records	Early childhood	Maternal exposure to benzene Paternal exposure to benzene	3 4	HR 0.22 (0.03–1.60) for gliomas HR 1.41 (0.51–3.90) for gliomas in the highest exposure category
<i>Ecological study</i>						
Air pollution	Danysh et al. [8], 2015	Concentrations by the US environmental protection agency about participant's residences	During diagnosis	1,3-Butadiene	590	IRR 1.10 (0.97–1.25) for (0.031–0.046 µg/m ³) concentration
					117	IRR 1.46 (1.05–2.01) for (0.031–0.046 µg/m ³) concentration in astrocytomas
				Benzene	599	IRR 1.07 (0.94–1.21) for (0.614–0.852 µg/m ³) concentration
				DMP in residences	657	IRR 1.20 (1.06–1.37) for (0.218–0.784 µg/m ³) concentration

* Means that the article has been also mentioned in another section. If tumour type is not specified it is all brain tumours.

Exp., exposure; Cd, cadmium; MBT, malignant brain tumours; CN, cranial nerves; BT, brain tumours; PNET, primitive neuroectodermal tumour; NA, not available; DMP, diesel particulate matter; HR, hazard ratio; IRR, incident rate ratio; PHA, polycyclic aromatic hydrocarbons.

analytical risk estimate for pesticides exposure during pregnancy was 1.73 (1.45–2.07), statistically significant, with no evidence of heterogeneity ($I^2 = 0\%$; online suppl. Fig. 3).

Results of exposure to pesticides during childhood or from prior to birth until BT diagnosis were mostly statistically not significant. Nevertheless, increases of risk were seen in 5 [9, 22, 26, 41, 42] out of 8 studies which assessed exposure during childhood [9, 22, 24–27, 41, 42]. These increases were seen in 2 studies of use of pesticides at home; 1 study of exposure to wood preservatives (53 cases and 746 controls) or home treated with pesticides once per year (8 cases and 96 controls) during childhood and risk of astrocytomas and 1 study of insecticides use by the father and risk of medulloblastomas or PNET (111 cases and 70 controls). A significantly increased meta-analytical effect estimate of 1.34 (1.15–1.56) was obtained for pesticide exposure during childhood. Heterogeneity was moderate ($I^2 = 60\%$; online suppl. Figure 3).

Another study that considered exposure starting 2 years before pregnancy until occurrence of BT in the offspring [43] found increased risks from use of herbicides

at home and in combination with paternal occupational exposure for atocytomas.

Eight studies analysed living on a farm and/or living with farm animals in different windows of exposure and BT risk. Five papers explored the association of childhood BT and mothers living and/or working on farms during pregnancy [19, 22, 23, 44, 45]. Increased risk was seen in 2 of them. A reduced risk was observed in 1 study ($n = 352$ cases) if mothers lived on a farm during pregnancy [46]. A non-statistically significant increased meta-analytical risk estimate was obtained for studies with mothers living/working on a farm during pregnancy (1.17 [0.69–1.98]). Heterogeneity was moderate ($I^2 = 63\%$; online suppl. Fig. 4).

Three articles explored mothers' contact with animals during pregnancy [22, 44, 45] and found increased risks of BT in their offspring assessing different exposures: cat scratches, contact with pigs or living on a farm with animals.

Seven articles [19, 22, 26, 39, 44–46] explored living on a farm during childhood as a risk factor for BT. Five of these articles suggested an increased risk, which was statistically significant in 3 (only one with large sample size)

[19, 26, 44]. Two other articles found a non-statistically significant reduced risk, based on small sample sizes, for BT in relation to living or working on a farm during childhood. As for exposure to farm environment during pregnancy living on a farm during childhood resulted in a non-statistical significant increased risk of 1.28 (0.98–1.68) with moderate heterogeneity of $I^2 = 46\%$ (online suppl. Fig. 4).

Four articles explored contact with farm animals and BT during childhood. Two articles found non-significantly increased risks: one for contact with sick pets (small sample) [26] and the other for exposure to any farm animal [44]. The other 2 articles found reduced risk in relation to contact with horses (small sample) [39], with birds (84 cases) or with goat and sheep (at least 3 years of exposure and 17 cases exposed) [46].

Non-Ionizing Radiation

Three articles [19, 42, 47] studied the association between extremely low frequency (ELF) exposure during pregnancy and BT risk.

Regarding the exposure to electrically heated waterbeds during pregnancy, 2 articles found non-significantly reduced risks (1 for astrocytomas and the other for BT in general) based on small sample sizes [19, 47]. No significant association was found for PNET either [19]. Regarding exposure to ELF from electrical blankets during pregnancy, 3 articles found non-statistically significantly increased risk [19, 42, 47].

Two studies focused on childhood ELF exposure [39, 47] and BT risk. One [39] found a non-significantly reduced risk for electric blanket and waterbed use based on very small numbers of cases ($n = 6$ and 1, respectively). In the other study, the ORs were close to one.

Two studies [48, 49] focused on radiofrequency (RF) exposures in childhood and BT were found. In the large multinational study [48], a non-significantly increased risk was found, with no evidence for an exposure response relationship between mobile phones use (which emits some ELF but mainly RF) and risk of BT. Use of mobile phones was low in this population, with an average duration of use of 2.7 years and lifetime cumulative time of use of only 35 h. Another study [49], which estimated average of exposure to RF from mobile phone base stations, found a non-statistically significant risk for exposure above the median, though the authors acknowledge several methodological limitations.

Three studies focused on the exposure to magnetic fields (MF) [50–52] from high-current power lines, elec-

tric heating sources or electric appliances at home during childhood. One [50] found a significantly increased risk for $\geq 0.4\mu\text{T}$ of MF in the children's bedroom (OR 10.9 [1.05–113] based on 3 cases and 1 control). Two [51, 52] studies found a non-statistically significant increased risk for exposure at home to high MF compared to low ones.

Parental Occupation

Fourteen case – control and 2 cohort studies were found studying the association between parental occupational exposures and BT risk. Seven articles examined job exposures before child's birth [53–61]. All of them found increased risks of BT in the offspring for some occupations or occupational exposures reported by parents (factory worker, machine repair, painter, among others), although some non-statistically reduced risks were found for some paternal job exposures, including unspecified chemicals, hydrocarbons, electromagnetic fields, or metals among others and for mothers whose jobs were related to medicine and science in general, activities related to aerospace, agriculture and farming. Only 1 study with a small sample found an inverse association for astrocytomas and paternal job in transportation industry (OR 0.1 [0.0–0.6]) [57].

Seven articles explored a wider time window of exposures [53, 54, 58–60, 62, 63]. Three of them found associations with some parental exposures during the 5 years before child's birth. Another [62], with a small sample size, found a suggestion of an increased risk in children younger than 9 years old, and a non-significantly reduced risk in children between 10 and 15 years old, for paternal employment in the aerospace industry at least 1 year prior to birth until time of child's diagnosis. Another [63], found a statistically significant increased risk of astrocytoma in children whose mothers used insecticides in their jobs (53 cases and 35 controls).

Two other studies [59, 60] found a suggestion for an increased risk from mothers exposed to diesel or chlorinated solvents at any time before child's birth; statistically significant only in one of them (17 cases and 29 controls).

When considering exposure during the postnatal period, 4 articles [57, 64–66] found increased risk of BT, statistically significant in 3 (father exposed to electrical repairing, ionizing radiation, agriculture, etc.). Additionally, 2 of the studies found a suggestion for a reduced risk for astrocytomas with occupational exposures to metals or paints.

One of the 2 cohort studies that assessed parental occupation during childhood [67] found an increased risk for parental pesticide exposure. The other cohort study

[68] found a non-significantly increased risk for paternal job exposure to benzene and a non-significantly reduced risk for maternal occupational exposure to benzene for astrocytomas. Exposures in this category were too heterogeneous to allow a formal meta-analysis.

Diet

Thirteen articles explored mother's diet during pregnancy and risk of BT in their offspring [22, 23, 25, 69–78]. Nine articles found an increased risk in relation to consumption of meat, which was statistically significant in 5 studies [23, 25, 69–71]. One of these studies [71] found an inverse association with BT and meat consumption during pregnancy if mothers also consumed multivitamin pills during all trimesters of pregnancy. Another article found a non-significantly reduced risk of BT related to meat consumption during pregnancy [22]. Other articles found reduced risk of BT in relation to consumption of iron supplements during pregnancy [72], consumption of vegetables [69, 73], grains or fresh fish [69] and non-fresh peaches or similar fruits [74]. The meta-analytical risk estimate for meat consumption during pregnancy was statistically significant and amounted to 1.51 (1.32–1.73) though with some heterogeneity ($I^2 = 44\%$; online suppl. Fig. 5).

Increased risks of BT were found for consumption of French fries [74], bacon [73], non-cured meat or fresh fish [69] or hot-dogs [75].

Two articles found a non-significantly increased risk related to consumption of high levels of nitrate during childhood (calculated from reported food consumption) [76] or hot-dogs consumption one or more times per week [75]. The meta-analysis for these articles related to exposure during childhood was non-statistically significant with a meta-OR of 1.27 (0.89–1.82) with no evidence of heterogeneity ($I^2 = 0\%$; online suppl. Fig. 5).

Another publication, not included in the tables, found an increased risk with increasing cured meat consumption during pregnancy in children without glutathione S-transferases theta 1 (OR 1.29 [1.07–1.57] for high cured meat intake per week) or reduced glutathione S-transferases mu 3 (OR 1.14 [1.03–1.26]). No increased risk was found for those with glutathione S-transferases theta 1 or normal glutathione S-transferases mu 3 levels [79].

Completeness of Methodological Information Reported

When analysing the methodological information reporting completeness for the articles included in this review (online suppl. Table 3), we observed that a 97% of

the articles included most of the 9 points that an article should include in the methodology section. The lowest score, due to missing information, was specifically concerning to participants' ethnicity, the recruitment period of the participants, number of controls matched per case, sample size and how missing data were managed. Sensitivity analyses were performed in few of the studies.

Discussion/Conclusion

Apart from ionising radiation and genetic syndromes, there are no established risk factors for BT in young people so far. Overall, there seems to exist some support in the literature for an association between BT and some specific environmental exposures. The early occurrence of BT suggests an important inherited component and that cancer initiating events might occur before conception, during foetal life or in early infancy [9], so the routes of exposure are diverse.

When considering exposures that can be associated with BT, it is particularly important to consider biological plausibility as the BBB protects the brain from toxicants. However, some toxicants have the capability of crossing the placenta and BBB, and some of them, like some heavy metals, have known neurotoxic effects [80]. Furthermore, radiation (both ionising and non-ionising) can deposit energy in the brain.

Parents can be exposed at work and/or in their daily lives (through diet, water consumption, air pollution, etc.) to DNA-modifying agents that could affect the germ line. Also, some toxicants can accumulate in the body (e.g., some metals that have the ability to bioaccumulate in bones or pesticides in fatty tissue), and children may be exposed during mother's pregnancy [13] or after birth through breastfeeding. Also, during the first 5 years of life of the child, hand-to-mouth activities can be another source of exposure.

There are suggestions that exposure to certain metals can occur through: dental amalgams [81, 82], childhood vaccines that previously used the ethyl mercury compound thiomersal as a preservative [81], environmental tobacco smoke (exposing especially to Cd), air pollution [81] or from young children eating paint chips in houses with old lead containing paints [83]. In our review, we found one article that suggested that cases with BT have higher concentrations of Cd in their biological samples than the control group [11], but no article assessing other metals, such as mercury, though

children can be exposed to methyl mercury through diet (fish). A follow-up study found higher levels of Cd and lead (Pb; hair and toenails samples) in parents and BT cases compared to parents and children of the control group (low levels of metals) [84], and this was especially the case in children <5 years of age. Since we found only 1 article dealing with heavy metals and BT risk, there is insufficient evidence to support an association with BT.

Other toxicants related to cancer are disinfection by-products, resulting from the treatment of drinking water from raw water containing organic matter. Trihalomethanes are the most studied disinfection by-products. We could not find any study about the relationship between BT risk and Trihalomethanes in young people, only few articles that suggest a possible association in adults [85]. Other water compound possibly related to cancer is nitrate, present in the water due to agricultural activity or wastewater treatment. Nitrate can be reduced to nitrite [86] compounds that are classified as probable human carcinogens. The articles found in this systematic review suggested an increased risk of BT in participants who consumed tap water with the presence of nitrite or nitrate. Nevertheless [10], an inverse association was found in Los Angeles region; the interpretation of this result is unclear, and is possibly due to low numbers of exposed: well water consumption was only reported by 20 participants of a total of 619. The limit of detection of nitrite and nitrate levels is different between studies, preventing comparison and interpretation of the results.

Another source of exposure to nitrite and nitrate, besides drinking water, can be diet. Nitrate is a common preservative for meat. The majority of the articles about diet suggested an increased risk with higher meat consumption and a suggestion of reduced risk related to consumption of fruits [74], vegetables, grains and fish for astroglial tumours [69], or iron supplements and astrocytoma [72].

Tobacco smoke (classified as group 1 “carcinogenic to humans” by the International Agency for Research on Cancer) [87] contains many toxic compounds known to be related to cancer risk. Some articles suggested a relationship between smoking tobacco and alterations in the germ cells [88], childhood BT or with leukaemia-lymphoma [89]. Some tobacco smoke compounds can cross the BBB and placenta barrier [28]. These theoretical considerations can be supported by the results of 2 case-control and 1 cohort study finding significantly increased risk of BT in offspring whose mothers smoked, 7 studies for mother’s ex-

posure to passive smoking and one for exposure during the postnatal period. This associations evidence the possible genotoxic effects to the foetus and newborns.

Living in urban areas with high traffic density implies being exposed to different chemicals from vehicle exhausts. In this review, only 3 articles were found studying this association; specifically, 2 of them assessed exposure to 1,3-butadiene [8, 12], with increased risks, though focusing on exposure during different periods of child development.

Some pesticides have been banned due to their negative health implications. Nevertheless, some of them are very persistent and stay in the environment (especially soil and water) for many years. The use of pesticides continues to be quite common, specifically in agriculture, to sustain the current productivity. Other pesticides used by professional applicators are currently used for the treatment and maintenance of homes made of wood, or to exterminate common pests such as termites or rats. Some of the articles reviewed suggested an increased risk of childhood BT related to exposure during childhood as well as during the pregnancy period, especially for parental handling of pesticides and for professional exterminations at home or garden. Children can be exposed substantially since the home is the place where children generally spend most of their time.

We also evaluated exposures that can occur when living on a farm. Living on farms or with farm animals can imply exposure to a wide range of chemicals and other agents, including viruses and bacteria, that might explain the different results obtained in these studies. The articles suggested increased risk when mothers lived on a farm during pregnancy and also for exposures to some specific animals (such as pigs). An increased risk was also found related to children who lived on a farm during their early childhood.

The increasing use of new technologies and electrical devices has a high appeal among young people, and children are exposed at young ages. It is likely that, over their lifetime, children will accumulate more exposure to non-ionising radiation than those who started using these technologies later in life. On the other hand, young people use, in general, more frequently messaging than calls to communicate, with a lower exposure to MF and RF received by the brain. In our systematic review, we found 6 articles that assessed exposure to non-ionizing radiation, and none of them found a significant association with BT, though most of them were based on small numbers and crude exposure estimates.

Another source of exposure of the child or the foetus can be parental occupational exposures. Children are indirectly exposed during pregnancy from exposures of mothers in their jobs or during the postnatal period, through particles of paint, radionuclides or other products the parents may bring home on their clothes. We found some publications that suggested an increased risk related to some specific parental jobs. However, due to the fact that studies did not explore the same occupations or the same exposure period, a comparison is difficult and the evidence is not clear.

This is, to our knowledge, the first systematic review that includes all studies relating BT in young people to environmental risk factors up to June 2018. Since BT aetiology is largely unknown, it is important to have a better knowledge on possible risk factors.

This review has some limitations. The majority of the studies included were case – control studies with exposure assessment mostly based on personal interviews (with the possibility of differential recall bias between cases and controls) without measurements and, in most instances, no information provided about the analysis of possible exposure – response relationships. Some studies explored a great number of risk factors with an elevated risk of chance findings. In general, results are difficult to compare because of small sample sizes, different risk factors studied with different exposure indicators and different periods of exposure, and in some instances different outcomes (specific types of BTs). This might affect the strength of the evidence for establishing possible associations. A meta-analysis was therefore only possible for a limited number of exposures that were fairly consistent across studies. Another limitation is that some potentially eligible articles could have been missed due to shortcomings in search terms and phrases and as well the different strategies used for the databases.

Overall, the studies reviewed suggest that exposure to heavy metals, passive smoking, water and air pollutants, use of pesticides and living on a farm with farm animals, meat consumption, during preconception, pregnancy or early infancy may increase the risk of BT in children and young adults. However, inconsistencies of results, the small numbers of exposed cases in many studies, often crude exposure assessment and lack of detailed exposure response analyses, no clear conclusion can be drawn at present. Larger scale studies with better exposure assessment are needed to evaluate possible associations between environmental risk factors and BT in young people, especially on exposure to heavy metals, tap water consumption, pesticides and

parental smoking. Furthermore, exposure to RF electromagnetic fields and MF should receive more attention.

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Statements of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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Author Contributions

All authors of this research paper have directly participated in the planning and execution of the work, the analysis of the articles found, the interpretation of the findings and the writing of the manuscript. All authors of this paper have read and approved the final version submitted.

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