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Environmental Risk Factors for Childhood Central Nervous System Tumors: an Umbrella Review

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Abstract

Purpose of Review Childhood central nervous system tumors (cCNSt) are the most common solid tumors in individuals under 20 years old, yet environmental risk factors are not well established. Therefore, we conducted an umbrella review to summarize the current literature on risk factors related to cCNSt.

Recent Findings Childhood exposure to ionizing radiation from medical devices was the strongest risk factor. There was evidence of positive associations with several other factors, including maternal age, birth weight, and pesticide exposure. Conversely, maternal folic acid supplementation during pregnancy and having childhood allergic conditions were inversely associated with cCNSt. Few studies assessed associations by cCNSt histological subtypes and none by molecular subtypes. Exposure assessments were limited to data linkages, parental recall via questionnaires, or measurements at diagnosis.

Summary Because cCNSt are highly heterogeneous, future research is needed to examine risk factors by molecular and histological subtypes and to apply novel, unbiased exposure assessments.

Keywords Childhood cancer · Pediatric cancer · Brain tumors · Environmental exposures

Introduction

Childhood central nervous system tumors (cCNSt) are the most common solid tumor diagnosed in children and adolescents [1]. Children with these tumors have relatively poor survival [2] compared to those with other pediatric malignancies, and those who survive often have multiple chronic health conditions [3, 4]. Genetics explain a small proportion of the variability as the few genome-wide association studies (GWAS) of cCNSt have identified a handful single nucleotide polymorphisms (SNPs) associated with inherited genetic risk [5–7]. These findings must also be replicated in larger populations and by tumor type. Additionally, because known cancer variants explain < 10% of diagnoses [8, 9], parental and childhood exposures to environmental factors are likely to play an important role in cCNSt etiology. Compared to adults, fetuses and children are vulnerable to environmental toxicants due to rapid growth during development, are disproportionately exposed to environmental toxicants when considering body weight to toxicant concentration ratio compared to adults, and do not have a fully developed blood–brain barrier which may allow toxicants to enter the CNS [10]. Conversely, some exposures may

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be protective and modifiable, which may inform public health interventions. To summarize the current literature on environmental risk factors of cCNSt, we conducted a comprehensive umbrella review of systematic reviews and meta-analyses published within the last five years, highlight existing knowledge on risk factors of cCNSt, and identify areas for additional characterization.

Methods

Literature Search

In accordance with Cochrane Handbook for Systematic Reviews of Interventions [11] and the JBI Manual for Evidence Synthesis best practices [12], we conducted a systematic search using controlled vocabulary and natural language. The search strategy encompassed the concepts of CNSt, prenatal, perinatal, and environmental risk factors and exposures, and a pediatric population (0–19 years). The search strategy was executed across MEDLINE via Ovid, Embase via Ovid, Scopus, Web of Science Core Collection, and the Cochrane Library via Wiley. The search (May 2022) was restricted to publications since 2017. Search and filter keywords are in Supplemental File 1. The protocol was registered a priori on June 17, 2022, in PROSPERO, an international database of prospectively registered systematic reviews (CRD42022337974).

Study Selection

The search results from all databases were compiled and deduplicated in Endnote X9 [13], then imported into Covidence [14]. Titles and abstracts were screened independently by two reviewers (LAW and TTH). Conflicts were resolved through consensus. Studies with children < 20 years of age with primary cCNSt were included; adults aged ≥ 20 years at diagnosis or children diagnosed with secondary cCNSt were excluded. Systematic reviews and meta-analyses were the study designs of focus, but primary research is cited as background where necessary.

After initial title/abstract screening, full-text reports were screened independently by two reviewers (LAW and TTH). Discrepancies were resolved through consensus. Reasons for exclusion at this phase are reported in Fig. 1 in accordance with PRISMA standards.

Data Collection

Data extraction forms were developed in Covidence by TTH and LAW and piloted before being further refined by LAW, TTH, and EW. Data were extracted from each of the 31 included studies independently by two authors (EW all articles, LAW $n = 16$ and TTH $n = 15$). Data extracted included studies' search strategies, exposures of interest, pre or postnatal exposure, and number of studies. For meta-analyses, effect estimates (odds ratios (ORs) or relative risk (RR) and 95% confidence intervals (95% CI)) were extracted as well as any assessments of publication bias. Findings are presented in Table 1.

Results

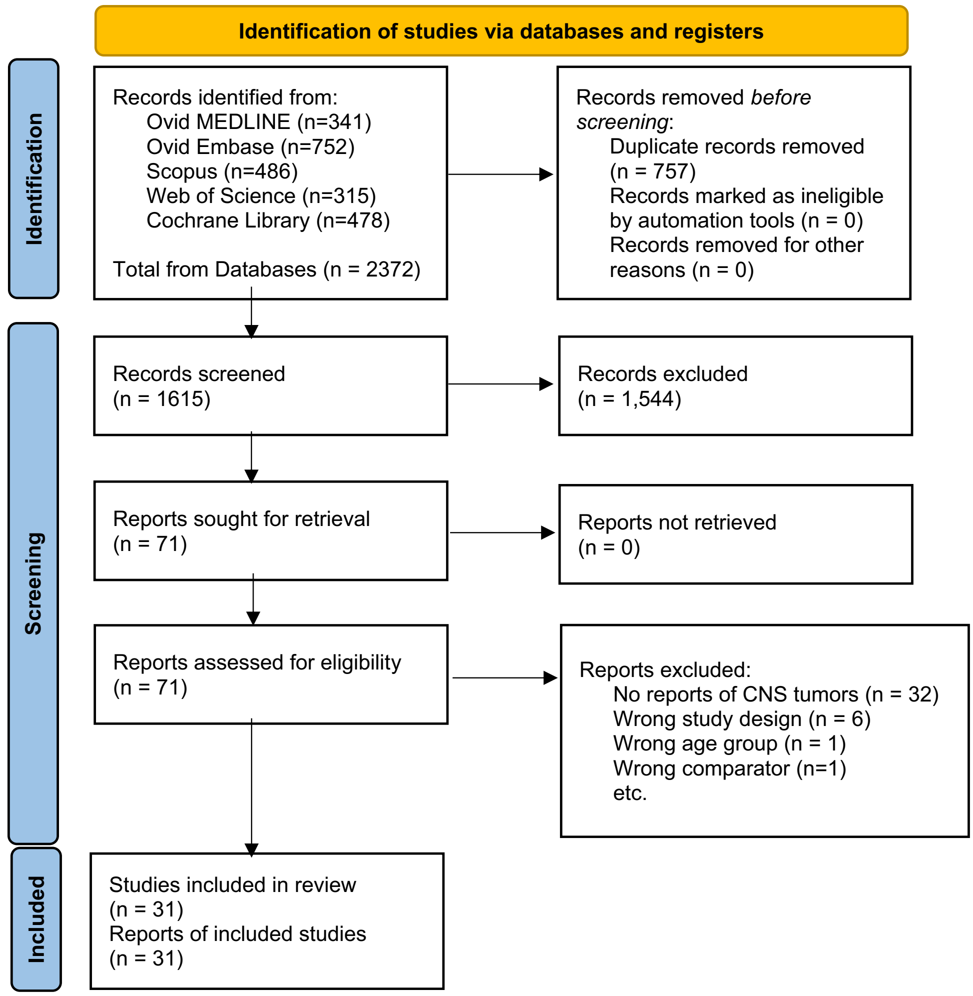
Demographic Factors

Nieblas-Bedolla et al. [15] reported higher cCNSt incidence rates in White and Asian children compared to other race/ethnicity groups (e.g., Hispanic and non-Hispanic Black) using data from 11 population-based registry studies including Surveillance, Epidemiology and End Results (SEER). While differences in parental characteristics (i.e., parental age at first birth as discussed herein [16]) may contribute to the underlying racial/ethnic differences in incidence, further research is needed to examine the extent to which these racial/ethnic differences are due to environmental exposures, sociocultural practices, and/or genetic ancestry. Parental age is another commonly explored risk factor for cCNSt due to increased germline mutations in older parental gametes among other mechanisms [18]. From a meta-analysis of six studies [19], risk of any cCNSt with each 5-year increase in maternal age was 1.07 (95% CI: 1.04–1.10) and varied by histology (ependymoma OR: 1.17, 95% CI: 1.07–1.29; astrocytoma OR: 1.10, 95% CI: 1.05–1.15; medulloblastoma OR: 1.04, 0.98–1.12). There was a null association for each 5-year increase in paternal age and cCNSt (OR: 1.01, 95% CI: 0.99–1.03). Finally, parental educational attainment often is a proxy for socioeconomic status. In a systematic review by Quach et al. [20], the authors note a paucity of studies on this topic and highlight a single case–control study [21] where increasing education was inversely associated with offspring cCNSt, particularly for 13–16 years of maternal education (versus > 17 years) and cCNSt (OR: 0.81, 95% CI: 0.69–0.96); however, a protective association was reported for astrocytoma for < 12 years (versus > 17 years) of education (OR: 0.70, 95% CI: 0.51–0.95). The overall findings were not replicated by Francis et al. [22] in California (13–15 years of maternal education cCNSt OR: 1.14, 95% CI: 1.01–1.28). Additional population-based studies of this association using more comprehensive socioeconomic status measures and an updated meta-analysis are necessary.

Diet

Dietary assessment is often fraught with recall bias. Nonetheless, maternal dietary intake has been examined in

Fig. 1 Flow diagram of systematic literature review and screen, following PRSIMA guidelines



various studies of cCNSt risk. In a meta-analysis of 12 studies by Zumel-Marne et al. [23], maternal meat consumption, including cured meats, was positively associated with offspring cCNSt (OR: 1.51,95% CI: 1.32–1.73). For meat intake during childhood, the meta-analyzed OR of two studies was 1.27 (95% CI: 0.89–1.82) [23]. Meta-analyses for other dietary components were not available, but there was a reported increased association of cCNSt with maternal consumption of French fries, bacon, non-cured meat, fresh fish, and hot dogs, or dietary N-nitroso compounds, as detailed by Zumel-Marne et al. [23] and Quach et al. [20]. Concerning gene by environment interaction, one study reported that maternal meat consumption during pregnancy among children born with glutathione S-transferase variation was positively associated with cCNSt [24].

Maternal Folate Intake

Folate can be ingested via folic acid supplementation or dietary intake and regulates DNA synthesis and repair thereby preventing DNA damage that can lead to tumor formation [25]. Two meta-analyses have summarized studies of maternal folate intake and cCNSt. In a meta-analysis of six studies from Wan Ismail et al. [26], the association between maternal folic acid supplementation and cCNSt was null (OR: 1.02, 95% CI: 0.88–1.19). Even though the included studies focused on supplementation, they likely did not uniformly and completely account for background folic acid fortification of flour, which varies by country [27]. In the meta-analysis by Chiavarini et al. [28], total maternal folate intake from 32 studies resulted in a protective association with offspring cCNSt (OR: 0.77, 95% CI: 0.67–0.88), which was present in selected cCNSt histological subtypes (embryonal tumors OR: 0.70, 95% CI: 0.54–0.90; miscellaneous intracranial/spinal tumors OR: 0.82, 95% CI: 0.68–0.99; low-grade gliomas [one study] OR: 0.55, 95% CI: 0.39–0.79), except astrocytoma (OR: 0.93, 95% CI: 0.63–1.38). When the authors considered folate source, they observed a protective association with dietary folate (OR: 0.76, 95% CI: 0.53–1.07) and folic acid supplementation (OR: 0.77, 95% CI: 0.66–0.90), contradicting the null findings by Wan Ismail et al. [26]. Folate intake preconceptionally or prenatally

Table 1 Results from the systematic reviews and meta-analyses for risk factors for childhood CNS tumors since 2017

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
Race/ethnicity	Nieblas-Bedolla, 2021	Jan 1, 2005 to July 15, 2020	SR	11	Birth/childhood	Race/ethnicity	Not reported	Higher incidence of CNS tumors among children who identify as White or Asian	Not applicable
Parental age	Domingues, 2022●	Through March 2022	SR and MA	8	Birth/childhood	Parental age (5-year increment)	33,847 cases/3,675,858 controls	5-year increase in maternal age Overall OR: 1.07 (95% CI: 1.04–1.10) Ependymoma OR: 1.17 (95% CI: 1.07–1.29) Astrocytoma OR: 1.10 (95% CI: 1.05–1.15) Medulloblastoma OR: 1.04 (95% CI: 0.98–1.12) 5- year increase in paternal age Overall OR: 1.01 (95% CI: 0.99–1.03)	No
Parental educational attainment	Quach, 2017	Did not specify	SR	1	Birth and childhood	Maternal education (years)	12,665 cases/39,472 controls	13–16 years OR: 0.81 (95% CI: 0.69–0.96) < 12 years astrocytoma OR: 0.70, 95% CI: 0.51–0.95)	Not applicable

Table 1 (continued)

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
Diet	Zumel-Marne, 2019●●	Until January 2019	SR	Not reported	Pregnancy Childhood	Maternal dietary intake Dietary intake	Not reported	Maternal consumption of meat (OR: 1.51 (95% CI 1.32–1.73) increased risk of cCNSt for maternal intake of French fries, bacon, non-cured meat or fresh fish, or hotdogs Reduced risk of cCNSt in relation to consumption of iron supplements during pregnancy, consumption of vegetables, grains or fresh fish, and canned fruit Increased risks of cCNSt were found consumption of high levels of nitrate during childhood (hot-dogs) one or more times per week (OR: 1.27, 95% CI 0.89–1.82)	Not applicable
	Quach, 2017	Did not specify	SR	Not reported	Pregnancy	Maternal meat intake	Not reported	Offspring who lacked certain GST variants demonstrated an increased risk for childhood brain tumor development in relation to maternal pregnancy meat intake	Not applicable
Maternal folate intake	Wan Ismail, 2019	1998 to Nov 1, 2018	SR and MA	6	Prenatal	Maternal folic acid supplementation	2665 cases, 7440 controls	OR 1.02 (95% CI: 0.88–1.19)	No

Table 1 (continued)

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
	Chiavarini, 2018	Up to Nov 27, 2017	SR and MA	32	Prenatal	Maternal folic acid intake	Not reported	Total folate OR: 0.77 (95% CI: 0.67–0.88) Embryonal tumors OR: 0.70 (95% CI: 0.54–0.90) Miscellaneous intracranial/spinal tumors OR: 0.82 (95% CI: 0.68–0.99) Low-grade gliomas [one study] OR: 0.55 (95% CI: 0.39–0.79) Dietary folate (OR: 0.76, 95% CI: 0.53–1.07) Folic acid supplementation (OR: 0.77, 95% CI: 0.66–0.90)	Yes, overall analysis (Egger $p = 0.036$) not Begg and Mazumdar test (p-0.339)
Birth order	Nguyen, 2018	Up to March 2018	SR and MA	19	Birth	Birth order	Not reported	2nd vs 1st born OR: 1.04 (95% CI: 1.01–1.07) 3rd vs 1st born OR: 0.98 (95% CI: 0.90–1.06) 4th vs 1st born OR: 0.85 (95% CI: 0.78–0.92)	No
Sibship size	Han, 2020	MEDLINE, and EMBASE inception until January 2020; Web of Science inception until July 2018	SR and MA	1	Childhood	Larger number of births	Not reported	RR:1.27 (95% CI: 1.06–1.52) From parent publication (Altieri et al. 2006) two siblings RR: 1.26, 95% CI: 1.10–1.45; three siblings RR: 1.41, 95% CI: 1.21–1.65; ≥4 siblings RR: 1.27, 95% CI: 1.06–1.52)	No

Table 1 (continued)

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
Seasonality of birth	Georgakis, 2017	To June 25, 2017	SR	10	0–18 years of age	Season of birth	Not reported	3 studies showed peaks in the period December to February, others showed no significant effects Astrocytoma (3/7) studies found a significant peak between October and February Ependymoma (2/6) clustering of ependymomas births in December to February Embryonal tumors 2 studies showed Statistically significant peaks in births during September to November	Not applicable
	Karalexi, 2020	1983–2015	Pooled analysis	N/A	0–14 years of age	Season of birth	6014 cases	0–4 years Winter: IRR: 1.11 (95% CI: 1.00–1.23) Boys, 0–4 years Winter: IRR: 1.16 (95% CI: 1.00–1.35) 5–14 years, girls Winter: IRR: 1.17 (95% CI: 1.00–1.37) 5–14 years, girls, Astrocytomas, Spring—IRR: 1.28 (95% CI: 1.04–1.58) Embryonal Winter: IRR: 1.33 (95% CI: 1.03–1.71) Summer: IRR: 0.73 (95% CI: 0.54–0.99)	Not applicable

Table 1 (continued)

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
Birth weight	Quach, 2017	Did not specify	SR	1 MA	Birth	Birth weight in grams	1801 cases	High birth weight (> 4000 g) was significantly associated with astrocytoma (OR: 1.38, 95% CI: 1.07–1.79) and medulloblastoma (OR:1.27, 95% CI: 1.02–1.60), not ependymoma (OR: 1.15, 95% CI: 0.65–2.04)	Not reported
Breastfeeding	Su, 2021	From inception to July 17, 2020	SR and MA	7	Infancy/duration of breastfeeding	Breastfeeding	475,579 individuals	Any versus none OR/RR: 0.96 (95% CI: 0.83–1.10) longest vs shortest duration OR/RR: 0.95 (95% CI: 0.79–1.14)	No
Drinking water	Picetti, 2022	Jan 1, 1990–Feb 28, 2021	SR and MA	3	Childhood	Nitrate in drinking water	540 cases, 801 controls	RR per 10 mg/L NO_3: 1.16, 95% CI: 0.64–2.11	Not reported
	Zumel-Marne, 2019●●	Up to Jan 2019	SR	1	3	Tap water consumption	Not reported	Largely null findings, varied by location for maternal well water intake during pregnancy Seattle OR: 2.6, 95% CI: 1.3–5.2; Los Angeles County OR: 0.2, 95% CI: 0.1–0.8	Not applicable
Allergies	Quach, 2017	Did not specify	SR	1	Childhood	Allergic conditions	272 cases/272 controls	Asthma (OR:0.55, 95% CI: 0.33–0.93) eczema (OR:0.52, 95% CI: 0.17–1.57)	Not applicable
Head injuries	Quach, 2017	Did not specify	SR	1	Childhood	Head injury	318/318	Medulloblastoma/PNET OR: 0.78 (95% CI: 0.40–1.50)	Not applicable

Table 1 (continued)

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
Air pollution	Buser, 2021	Jan 1, 2010 to Feb 10, 2021	SR	2	9 months before birth to diagnosis	Outdoor benzene	Not reported	Exposure during pregnancy is significantly associated with medulloblastoma	Not applicable
	Buser, 2021	Jan 1, 2010 to Feb 10, 2021	SR	2	At diagnosis	Benzene, 1,3-butadiene, diesel particulate matter	Not reported	No association with benzene Positive associations with other pollutants and certain CNS tumor subtypes	Not applicable
	Zumel-Marne, 2019●●	Up to Jan 2019	SR	2	Prenatal or first year of life	Acetaldehyde, 1,3-butadiene, PAH, ortho-dicholorobenzene, lead	20 to 38/16,680 to 27,189	Pregnancy: significant positive associations (range of ORs: 1.44–2.23) with PNET and medulloblastoma First year of life: positive associations (range of ORs: 1.40–3.27) with PNET and astrocytomas	Not applicable
	Zumel-Marne, 2019●●	Up to Jan 2019	SR	2	At birth	Maternal residential high roadway density	9/1,173 15/591	OR: 3.04 (95% CI: 0.38–24.07) for PNET OR: 4.23 (95% CI: 1.20–14.88) for ependymoma	Not applicable
Metals	Zumel-Marne, 2019●●	Up to Jan 2019	SR	1	Childhood	Cadmium measured in serum, urine, hair, nails	4/350	Cd concentration in cases is greater than controls ($p < 0.001$)	Not applicable
	Meng, 2020	up to July 1, 2019	MA	3	prenatal	Parental lead exposure	Not reported	OR: 1.17 (95% CI: 0.99–1.34)	No
Parental smoking	Quach, 2017	Did not specify	SR	1 MA	During pregnancy	Maternal smoking	Not reported	RR: 1.05 (95% CI: 0.90–1.21)	Not applicable
	Zumel-Marne, 2019●●	Up to Jan 2019	MA	20	During pregnancy	Maternal smoking	~837/2286	OR: 1.09 (95% CI: 1.00–1.18)	Not reported
	Zumel-Marne, 2019●●	Up to Jan 2019	MA	17	During pregnancy	Maternal exposure to passive smoke	~652/903	OR: 1.32 (95% CI: 1.12–1.55)	Not reported
	Oldereid, 2018	Up to Jan 1, 2017	MA	14	During pregnancy	Paternal smoking	Not reported	OR: 1.12 (95% CI: 1.03–1.22)	Not reported

Table 1 (continued)

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
	Zumel-Marne, 2019●●	Up to Jan 2019	MA	3	Childhood	Passive smoke	~605/1138	2 studies reported no association; 1 reported a statistically significant increased risk	Not reported
Radiation–ionizing	Little, 2022	up to May 16, 2021	MA	1	During pregnancy	Medical diagnostic exposures: Lower dose risk estimates (<0.1 Gy) Higher dose risk estimates (<1 Gy)	844 cases	ERR/Gy = 70.0 (−229, 369) ERR/Gy = 70.0 (−229, 369)	Not reported
	Wakeford, 2021	through 14 September 2020	MA	20	During pregnancy	X-rays	289/4680	RR: 1.13 (95% CI: 0.97, 1.31)	Not reported
	Abalo, 2021	Jan. 1, 2000, to July 31, 2019	MA	3	During pregnancy	Diagnostic radiation exposure (X-rays and CT scans)	3461 cases and 7924 controls	OR: 0.93 (95% CI: 0.68–1.28)	No
	Wit, 2021	Jan 2007 and Sept 2018	SR	4	During pregnancy	X-rays	~863/1172	No statistically significant association	Not applicable
	Ruano-Ravina, 2018	up to Nov 21, 2016	SR	7	Childhood	Radon	~9161/22,382	Only 2 of 8 studies reported exposure was significantly associated with higher risk	Not applicable
	Quach, 2017	Did not specify	SR	1	Childhood	X-rays	318 cases, 318 matched controls	No association with medulloblastoma or PNET	Not applicable
	Abalo, 2021	Jan. 1, 2000, to July 31, 2019	MA	3	Childhood	X-rays CT scans	11,393,070 total in pooled analyses; 478 brain tumors	X-rays: no association CT: ERR_{pooled} = 9.1 Gy-1 (95% CI: 5.2–13.1)	No
	Berrington de Gonzalez, 2021	Up to Jan 25, 2021	MA	7	Childhood	CT scans at any age	Not reported	ERR/100 mGY: 0.79 (95% CI: 0.47–1.11)	Not reported
	Huang, 2020	Jan 1990 to Nov 2018	MA	5	Childhood	CT scans	Not reported	RR: 1.54 (95% CI: 0.84–2.45)	No

Table 1 (continued)

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
	Sheppard, 2018	up to March 13, 2017	SR	5	Childhood	Head CT scans	995,091 exposed	RR: 2.29 (95% CI 1.66–2.93) ERR: 1.29 (95% CI 0.66–1.93)	Not applicable
	Hauptmann, 2020	2006 to 2017	SR	2	Childhood	Low-dose ionizing radiation (mean cumulative dose < 100 mGy)	Not reported	2 reported elevated risk but only 1 was statistically significant	Not applicable
	Little, 2022	Up to May 16, 2021	MA	7	Childhood	Medical diagnostic exposures: Lower dose risk estimates (< 0.1 Gy) higher dose risk estimates (< 1 Gy)	1486 cases	< 0.1 Gy—ERR/Gy: 6.81 (95% CI: 0.58,13.04) < 1 Gy—ERR/Gy: 6.87 (95% CI: 1.02,12.72)	Not reported
Radiation–non-ionizing	Zumel-Marne, 2019●●	Up to Jan 2019	SR	3	During pregnancy	Electrical blanket, heated waterbed	Range of 1 to 55/18 to 485	No significant associations	Not applicable
	Carpenter, 2019	Did not specify	SR	2	During pregnancy	ELF radiation	Not reported	Increased risk for astroglial tumors with maternal ELF or magnetic field exposure	Not applicable
	Su, 2018	Up to Dec 2017	MA	8	During pregnancy	Maternal exposure ELF-MF radiation	Not reported	OR: 1.16 (95% CI: 1.06–1.26)	No
	Su, 2018	Up to Dec 2017	MA	12	During pregnancy	Paternal exposure to ELF radiation	Not reported	OR: 1.15 (95% CI: 0.98–1.34)	No
	Carpenter, 2019	Did not specify	SR	1	Childhood	ELF radiation	Not reported	Increased risk	Not applicable
	Zaki, 2020	Up to Nov 2018	SR	1	Childhood	EMFs	174/4,923	OR: 1.14 (95% CI: 0.83, 1.55)	Not applicable
	Zumel-Marne, 2019●●	Up to Jan 2019	SR	7	Childhood	Electrical blanket, heated waterbed, magnetic fields, phones, RF exposure	Range of 1 to 194 / 1 to 4,923	1 study found significantly increased risk with magnetic field in child's bedroom (OR: 10.90, 95% CI: 1.05–113 for ≥ 0.4 μT)	Not applicable

Table 1 (continued)

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
	Buser, 2021	Jan 1, 2010 to Feb 10, 2021	SR	3	Childhood	Magnetic fields, diagnostic radiological procedures	Not reported	1 study found positive association, 1 no association with magnetic fields, 1 study found no association with diagnostic procedures	Not applicable
	Roosli, 2019	up to Dec 31, 2017	SR	2	Childhood	Mobile phone use	Not reported	1 study suggested notable increases in astrocytoma risk, another study suggests no association	Not applicable
Pesticides	Quach, 2017	Did not specify	SR	1 SR/MA	During pregnancy	Parental pre-natal pesticide exposure	Not reported	Maternal OR: 1.37 (95% CI: 1.08–1.76) Paternal OR: 1.49 (95% CI: 1.23–1.79)	Not applicable
	Feulefack, 2021	1 Jan 1966 and 31 Dec 2020	MA	24	During pregnancy	pesticide exposure	Not reported	OR: 1.31 (95% CI: 1.17–1.46)	No
	Van Maele-Fabry, 2017●	1966 to 28 February 2017	MA	4	During pregnancy	Residential pesticide exposure	Not reported	Glioma OR: 1.31 (95% CI: 1.08–1.59) Embryonal OR: 1.04 (95% CI: 0.69–1.57) Herbicide OR: 1.28 (95% CI: 0.97–1.70) Insecticide OR: 1.26 (95% CI: 1.04–1.54)	No
	Zumel-Marne, 2019●●	Up to Jan 2019	MA	7	During Pregnancy	Parental exposure to pesticides	~580/791	OR: 1.73 (95% CI 1.45–2.07)	Not reported
	Quach, 2017	Did not specify	SR	1 SR/MA	Childhood	Paternal and childhood post-natal pesticide exposure	Not reported	Paternal OR: 1.66 (95% CI: 1.11–2.49) Childhood OR: 1.16 (95% CI: 1.01–1.32)	Not applicable
	Feulefack, 2021	1 Jan 1966 and 31 Dec 2020	MA	17 20 8	Childhood	Pesticide exposure after birth, occupational exposure, residential exposure	Not reported	After birth OR: 1.22 (95% CI: 1.03–1.45) Occupational OR: 1.17 (95% CI: 0.99–1.38) Residential OR: 1.31 (95% CI: 1.11–1.54)	No

Table 1 (continued)

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
	Van Maele-Fabry, 2017●	1966 to 28 Feb 2017	MA	18 2 2 7 3	Childhood	Residential pesticide exposure, flea and tick pesticide exposure	Not reported	Any pediatric brain tumor OR: 1.26 (95% CI: 1.13–1.40) Glioma OR: 1.05 (95% CI: 0.79–1.39) Embryonal OR: 1.12 (95% CI: 0.74–1.69) Any pediatric brain tumor age 0–15 years OR: 1.30 (95% CI: 1.11–1.52) Any pediatric brain tumor, flea and tick pesticide exposure OR: 1.46 (95% CI: 1.05–2.05)	No
	Zumel-Marne, 2019●●	Up to Jan 2019	MA	10	Childhood	Pesticides	~639/2992	OR: 1.34 (9% CI: 1.15–1.56)	Not reported
	Iqbal, 2022	2010 to 2020	SR	4	Childhood	Residential and domestic pesticide exposure	~24,740 participants	3 of 4 studies had evidence of significant increased risk for residential pesticide exposure	Not applicable
	Buser, 2021	Jan 1, 2010 to Feb 10, 2021	SR	2	Childhood	Pesticides	Not reported	A study reported exposure to crops is associated with an increased risk. Another observed higher pyrethroid metabolites in children with CNS tumors than those without	Not applicable
Farm residence and exposures	Zumel-Marne, 2019●●	Up to Jan 2019	MA	5	Pregnancy	Living on a farm	~570/314	OR: 1.17 (95% CI: 0.69–1.98)	Not reported
	Zumel-Marne, 2019●●	Up to Jan 2019	MA	7	Childhood	Living on a farm	~418/788	OR: 1.28 (95% CI: 0.98–1.68)	Not reported

Table 1 (continued)

Exposure	Reference, year	Search range	Study type	No. of studies	Exposure period	Specific exposure	No. of cases/no. of controls	Results	Evidence of publication bias as reported by authors
Parental occupation	Zumel-Marne, 2019●●	Up to Jan 2019	SR	10	Preconception	Parental occupational exposure	~1254/2756	Some studies found increased risks of cCNSt in the offspring for some occupations or occupational exposures reported by parents	Not applicable
	Zumel-Marne, 2019●●	Up to Jan 2019	SR	4	Childhood	Parental occupational exposure	~265/1547	4 studies found increased risk of BT, and this was statistically significant in 3 studies. 2 studies found reduced risk for astrocytomas with occupational exposure to metals or paints	Not applicable

Zumel-Marne et al. [23] is a comprehensive systematic review and meta-analysis, summarizing the literature on risk factors related to cCNSt. Domingues et al. [19] is a well-powered study, meta-analyzing associations of parental age, both maternal and paternal, and cCNSt overall and by histological types. Van Maele-Fabry et al. [94] is a comprehensive meta-analyses of pesticide exposure in relation to cCNSt, considering timing, age at diagnosis, pesticide type, and cCNSt type reduced cCNSt risk by > 20% [28]. Overall, the Chiavarini et al. [28] findings from the 32 studies in their meta-analysis suggest total folate intake may be a modifiable risk factor for cCNSt.

Birth Order

Higher birth order is hypothesized to reduce cancer risk by (1) increasing immune function following acquisition of infections from older siblings, (2) decreasing fetal maternal hormone exposure in higher birth order children with low interpregnancy intervals [29], and (3) increasing frequency of microchimerism whereby maternal cells remain in the child [30] at higher concentrations in later born children. Nguyen et al. [31] conducted a meta-analysis of 16 case–control and three cohort studies for birth order and cCNSt. Compared to first born, higher risk of cCNSt was observed among second born (OR: 1.04, 95% CI: 1.01–1.07), but not third born (OR: 0.98, 95% CI: 0.90–1.06), and an inverse association among fourth born (OR: 0.85, 95% CI: 0.78–0.92). More work is needed to characterize the relationship between birth order and age at diagnosis to properly estimate associations between birth order and cCNSt.

Sibship Size

Higher sibship impacts cCNSt risk via increased exposure to infectious agents, though studies are limited. As reviewed by Han et al. [32], increasing sibship elevated the risk of cCNSt in a Swedish registry study of 13,613 children (two siblings RR: 1.26, 95% CI: 1.10–1.45; three siblings RR: 1.41, 95% CI: 1.21–1.65; ≥ 4 siblings RR: 1.27, 95% CI: 1.06–1.52) [33]. The association varied by histology (ependymoma ≥ 4 siblings RR: 1.83, 95% CI: 1.12–3.00; astrocytoma three siblings RR: 1.36, 95% CI: 1.06–1.74). However, these analyses were not adjusted for maternal age at birth, which could drive underlying associations as it is a cCNSt risk factor as discussed above.

Seasonality of Birth

Often used as a proxy for prenatal exposures to pesticides or patterns of infectious diseases [34], seasonality of birth has been explored in association with cCNSt as reported by Georgakis et al. [34]. A meta-analysis was not performed as risk estimates were not uniformly available; however, in studies with risk estimates, results were inconclusive and varied by country and cCNSt histology. In a recent pooled analysis by Karalexi et al. of 16 cancer registries from 14 South and Eastern European countries [35], there was an elevated incidence of cCNSt in winter-born children (incidence rate ratio (IRR): 1.06, 95% CI: 0.99–1.14) and this was significant for embryonal tumors (IRR: 1.13, 95% CI: 1.01–1.27) and among males with embryonal tumors (IRR: 1.24, 95% CI: 1.05–1.46). For girls, there was a higher incidence of astrocytoma for those born in spring (IRR: 1.23, 95% CI: 1.03–1.46). These findings remain to be validated in other populations.

Birth Weight

Low and very high birth weight is an established risk factor for various childhood malignancies [36] that may increase the risk of cCNSt by (1) higher cell counts in larger baby's brains increasing mitotic events leading to more somatic mutations [37] or (2) altering maternal hormones and growth factors encouraging rapid fetal growth [38, 39], which could permit carcinogenesis. As detailed by Quach et al. [20], in a 2008 meta-analysis [40], high birth weight (> 4000 g) was associated with astrocytoma (OR: 1.38, 95% CI: 1.07–1.79), and medulloblastoma (OR: 1.27, 1.02–1.60), but not ependymoma (OR: 1.15, 95% CI: 0.65–2.04). The high birth weight findings were confirmed in a 2017 meta-analysis [41] and birth weight < 2500 g was also associated with medulloblastoma/PNET (OR: 1.19, 95% CI: 1.02–1.39). The results suggest birthweight may underly etiologic heterogeneity by cCNSt histology.

Breastfeeding

Breastfeeding may confer long-term health benefits to the mother, such as reduced risk of developing breast [42] and ovarian [43] cancers. Additionally, it is hypothesized that breastfeeding bolsters immune function in offspring, thereby limiting the likelihood of developing cancer. However, studies in breastfed offspring have largely been equivocal. In a 2021 meta-analysis of seven studies [44], there was no association between breastfeeding and cCNSt (any versus non/occasional OR: 0.96, 95% CI: 0.83–1.10; longest versus shortest duration [six studies] OR: 0.95, 95% CI: 0.79–1.14). There was no variation in risk by histology. More detailed approaches to testing the breastfeeding hypothesis are needed, but results thus far suggest a limited role for breastfeeding in cCNSt risk reduction.

Drinking Water

Contaminated tap water is hypothesized to impact disease etiology in humans. As children undergo rapid growth until puberty, they may be particularly susceptible to carcinogenic contaminants in tap water. Studies of drinking water and cCNSt are few, and results have been mixed. As reviewed by Zumel-Marne et al. [23], studies examining well water during pregnancy and cCNSt were null but varied by location (Seattle OR: 2.6, 95% CI: 1.3–5.2; Los Angeles County OR:

0.2, 95% CI: 0.1–0.8) suggesting regional variation in well water composition may be important; however, the study did not adjust for important risk factors beyond age, sex, and region.

Nitrate and nitrite, byproducts of agricultural runoff and industrial waste, are ground water contaminants. These compounds may to impact carcinogenesis by forming nitrosamines and nitroso compounds upon metabolization, which are considered probable carcinogens (Group 2A) by the World Health Organization [45]. In a meta-analysis of three studies by Picetti et al. [46], there was an elevated, non-significant risk of cCNSt (RR: 1.16, 95% CI: 0.64–2.11) per 10 mg/L increase in nitrate in drinking water. Larger, population-based studies covering this topic are necessary.

Postnatal Allergies

Allergic conditions, including asthma and eczema, have been examined in association with cCNSt as summarized by Quach et al. [20]. Mechanisms underlying allergies and cancer posit the presence of allergies may protect from cancer as the immune system is in an elevated state of surveillance and can disrupt carcinogenic processes before tumor detection [47]. In the study of asthma, eczema, and cCNSt [48], asthma protected against cCNSt (OR: 0.55, 95% CI: 0.33–0.93) while a suggested protective effect was observed for eczema (OR: 0.52, 95% CI: 0.17–1.57). Although the asthma findings agree with a meta-analysis of allergies and adult glioma [49], confirmatory pediatric studies with complete allergic history, including maternal allergies during pregnancy, and adequate sample sizes are needed.

Head Injuries

Head injuries potentially inflict damage to the brain tissue and impact cCNSt development. As Quach et al. [20] reported, the summation of existing studies are inconclusive. A Children's Oncology Group study concluded there was no association between head injury and medulloblastoma/PNET development, but sample size was limited thereby impacting their precision (OR: 0.78, 95% CI: 0.40–1.50) [50]. Studies concerned with the severity of injury, timing, and histologic types of cCNSt are necessary; however, they could be confounded by CT scan exposure as discussed below.

Air Pollution

Air pollutants can cross the placenta leading to oxidative stress, neurotransmitter imbalance, neuroinflammation, and mitochondrial dysfunction in the developing brain impacting neurodevelopment and contributing to carcinogenesis [51, 52]. Two systematic reviews identified four studies (three case–control, one ecologic) that examined air pollution and cCNSt [23, 53]. The four studies considered different exposure time points (i.e., pregnancy, first year of birth, childhood) and exposures (i.e., proximity to highways or specific air pollutants: 1,3-butadiene, benzene, diesel particulate matter, acetaldehyde, polycyclic aromatic hydrocarbons, ortho-dichlorobenzene). As reviewed in Zumel-Marne et al. [23] and a study identified in Buser et al. [53], air pollutants during pregnancy were associated with PNET (OR range: 2.23–3.04 [54, 55]; most precise OR [acetaldehyde]: 2.30, 95% CI: 1.44–3.67) and medulloblastomas (OR range: 1.30–1.44; most precise OR [polycyclic aromatic hydrocarbon]: 1.44, 95% CI: 1.15–1.80) [54, 56].

There is suggestive evidence that childhood exposures to air pollutants may elevate overall risk of cCNSt, as air pollution exposure in the first year of life has been associated with cCNSt (OR range: 1.78–3.27 [47, 50]; most precise OR [1,3-butadiene]: 3.15, 95% CI: 1.57–6.32). Another study [57] identified by Buser et al. [53] reported mixed findings in which those in the 2nd quartile of exposure to diesel particulate matter at diagnosis had significantly higher risk (IRR: 1.20, 95% CI: 1.06–1.37) but not those in the 3rd or 4th quartile of exposures (3rd vs 1st IRR: 1.03, 95% CI: 0.90–1.18; 4th vs 1st IRR: 0.90, 95% CI: 0.78–1.04). We summarize the literature by major histological subtypes. For astrocytomas, Zumel-Marne et al. [23] reported increased risk with airborne lead exposure during first year of life (OR: 1.40, 95% CI: 0.97–2.03), Danysh et al. [57] reported increased risk with 1,3-butadiene or diesel particulate matter at diagnosis with non-juvenile pilocytic astrocytoma (IRR range: 1.22–1.69; most precise IRR [medium vs low diesel particulate matter]: 1.42, 95% CI: 1.05–1.94), and Raaschou-Nielsen et al. [56] reported null associations with benzene during childhood (RR: 1.0, 95% CI: 0.7–1.3). The literature with medulloblastomas is inconclusive as Raaschou-Nielsen et al. reported null associations with benzene (RR: 1.0), von Ehrenstein et al. did not identify any significant associations with air pollutants but consistently reported elevated ORs with polycyclic aromatic hydrocarbons (PAHs) including benzene (OR range: 1.08–1.50; most precise OR [dibenz[a,h] anthracene]: 1.20, 95% CI: 0.84, 1.72), and Danysh et al. reported significant with exposure to diesel particulate matter in the 2nd quartile (vs 1st) (IRR: 1.46, 95% CI: 1.01–2.12) but not in the 3rd or 4th quartile of exposures (3rd vs 1st IRR: 0.95, 95% CI: 0.63–1.45; 4th vs 1st IRR: 1.25, 95% CI: 0.83–1.88) [57]. For ependymomas, only Zumel-Marne et al. reported elevated risk with mother lived within 500 m of a major roadway at birth (OR: 3.08, 95% CI: 0.91–10.42) [23]. Additional, larger studies are warranted to confirm these observations.

Metals

Metals can cross the placenta and blood–brain barrier [58, 59] leading to oxidative stress and epigenetic alterations [60], which may lead to carcinogenesis. A systematic review identified one study of cCNSt cases ($n = 4$) that had higher levels of cadmium during childhood across blood, urine, scalp hair, and nails [23]. Meng et al. meta-analyzed three case–control studies of parental lead exposure during pregnancy (residential or occupational) [61] and reported elevated the odds of offspring cCNSt (OR: 1.17, 95% CI: 0.99–1.34). Larger studies of parental and childhood metal exposures and cCNSt are needed.

Parental Smoking

Smoking exposes individuals to several carcinogens and maternal smoking during pregnancy adversely affects offspring development [62]. Three publications were identified summarizing the literature on maternal smoking during pregnancy, passive smoke exposure during pregnancy for mothers, and offspring postnatal exposure.

The systematic review by Quach et al. [20] identified a 2002 meta-analysis, where maternal smoking during pregnancy did not impact offspring cCNSt risk (RR: 1.05, 95% CI: 0.90–1.21) [63]. Zumel-Marne et al. [23], published an updated meta-analysis, including 20 articles of maternal smoking during preconception or pregnancy and reported an elevated risk of offspring cCNSt (OR: 1.09, 95% CI: 1.00–1.18).

Zumel-Marne et al. also meta-analyzed 17 studies examining between maternal passive smoking exposure during pregnancy and cCNSt where maternal exposure significantly increased offspring cCNSt risk (OR: 1.32, 95% CI: 1.12–1.55) [23]. Oldereid et al. [64] published a meta-analysis examining paternal smoking during pregnancy, a proxy for maternal exposure to passive smoke and/or paternal smoking during conception, and offspring cCNSt risk. From the meta-analysis of 14 case–control studies, they reported a significantly increased risk for paternal smoking during pregnancy and offspring cCNSt (OR: 1.12, 95% CI: 1.03–1.22) [64]. Of these three publications, only Zumel-Marne et al. considered offspring exposure to passive smoke and found that two reported no association and one reported a significantly increased risk of cCNSt following passive smoke exposure [23].

Ionizing and Non-ionizing Radiation

We identified 16 meta-analyses or systematic reviews examining radiation exposure and cCNSt risk. Nine examined ionizing radiation, six examined non-ionizing radiation, and one summarized ionizing and non-ionizing radiation. Below we summarize the literature on radiation and cCNSt by type of radiation and timing of exposure.

Ionizing radiation can remove electrons from atoms when it passes through the body, potentially altering the cells within the body, which may lead to tumor development [65]. Sources of ionizing radiation can be natural (e.g., radon, cosmic, solar) or man-made (e.g., medical examination devices). Prenatal exposure to ionizing radiation was identified in four studies [66–69] that examined exposure to ionizing radiation from X-rays or CT scans during pregnancy. Overall, there was weak evidence that prenatal exposure was associated with cCNSt risk in offspring (RR range: 1.13–1.33; most precise RR: 1.13, 95% CI: 0.91–1.39; ERR/Gy: 70, 95% CI: −229, 369) [66–69].

We identified eight publications on childhood exposure to ionizing radiation, radon (one article) and medical examination devices (e.g., X-rays and CT scans [seven articles]). The radon systematic review summarized two of eight publications reporting higher risk of cCNSt [70]. One measured radon in water (RR: 1.28, 95% CI: 1.00–1.62) [71] and the other had relatively low exposure levels (mean radon = 27 Bq/m^3) that likely failed to represent the target population (OR: 3.85, 95%CI: 1.26–11.85) [72].

Medical examination devices emit different doses of ionizing radiation that varies by body location [73]. X-rays emit the lowest doses, ranging from 0.001 mSv (bone density test) to 0.4 mSv (mammogram) [73]. CT scans emit higher doses, ranging from an average of 2 mSv (head scan) to 16 mSv (angiogram) [73]. Quach et al.'s [20] reported that X-rays taken during childhood were not associated with cCNSt (OR range: 0.5–2.5) [50], which was confirmed in Abalo's et al.'s meta-analysis ($OR_{pooled} = 0.93$, 95% CI: 0.68–1.28) [68]. Conversely, there is evidence that postnatal CT scans significantly increased the risk of cCNSt (ERR range: 7.9–9.1 Gy; most precise ERR: 7.9 Gy, 95% CI: 4.7–11.1; RR range: 1.54–2.29; most precise RR: 1.54, 95% CI: 1.66–2.93) [68, 74–76]. Two publications examined radiation dose and cCNSt risk. Hauptmann et al. systematically reviewed two studies, both which reported an elevated cCNSt risk, but only one [77] was significant (ERR/mGy: 0.023 to 0.019, 95% CI: 0.008–0.043) [78]. In the meta-analysis of three studies, Little et al. reported an ERR/Gy of 6.81 (95% CI: 0.58–13.04) per unit of absorbed dose of radiation and risk of cCNSt [66]. In summation, dose of ionizing radiation exposure during childhood is a strong risk factor of cCNSt.

Non-ionizing radiation does not have enough energy to remove electrons from atoms and cause DNA damage, but the International Agency of Research on Cancer (IARC) has classified it as a possible carcinogen [79, 80]. Sources of non-ionizing radiation include microwaves, wireless devices, and infrared radiation in heat lamps [65]. Prenatal exposure to non-ionizing radiation was assessed in one meta-analysis and two systematic reviews. Zumel-Marne et al. identified three studies that examined electric blanket use during pregnancy with non-significant associations with astrocytomas, medulloblastomas, and PNET (OR range: 1.2–2.02) [23]. Similar results were observed with electrically waterbeds [23].

Maternal occupational exposure to extremely low frequency (ELF) radiation may be associated with risk of offspring cCNSt. Carpenter et al. identified two studies [81], which were included in Su et al.'s meta-analysis that reported maternal and paternal exposure to ELF-magnetic fields (MF) were associated with cCNSt (maternal OR: 1.16, 95% CI: 1.06–1.26; paternal OR: 1.15, 95% CI: 0.98–1.34) [82].

Five systematic reviews were identified summarizing the literature on postnatal exposure to non-ionizing radiation and cCNSt risk. Zumel-Marne et al. [23] included seven studies, of which three had limited evidence of childhood exposure to ELF-MF affecting risk of cCNSt [83–85], two reported null findings of childhood use of electric blankets or heated waterbeds and cCNSt [86, 87], and two evaluated radiofrequency radiation (including mobile phone use) and reported elevated but non-significant risk of cCNSt [88, 89]. Buser et al. identified two additional studies that examined electric or magnetic fields in relation to cCNSt, and neither study reported an association [53]. In Roosli et al.'s systematic review, a study reported notable increases in cCNSt risk with wireless phone use < 20 years of age for astrocytoma; however, the incidence of astrocytoma, which has remained stable, does not match the higher prevalence of wireless phone use in children < 20 years old [90]. Overall, there is lacking evidence that postnatal exposure to non-ionizing radiation impacts cCNSt risk.

Pesticides

Pesticides contain a mixture of chemicals that may alter the developing brain and be carcinogenic [91, 92]. We identified six publications on pesticides and cCNSt risk, of which four examined prenatal exposure and six examined childhood exposure. For prenatal exposures, Quach et al. [20] identified a 2011 meta-analysis [93] that reported only paternal prenatal exposure was associated with cCNSt (OR: 1.49, 95% CI: 1.23–1.79). The three other studies were meta-analyses and reported significantly increased risk of cCNSt with any parental exposure (OR range: 1.31–1.73) [23, 94, 95]. Van Maele-Fabry et al. [94] reported prenatal residential pesticide exposure increases glioma risk (OR: 1.31, 95% CI: 1.08–1.59) but not embryonal tumors (OR:1.04, 95% CI: 0.69–1.57). Elevated cCNSt risk was observed with prenatal exposure to herbicides (OR: 1.28, 95% CI: 0.97–1.70) and insecticides (OR: 1.26, 95% CI: 1.04–1.54) [95].

Childhood exposure to pesticides was associated with cCNSt (RR: 1.16, 95% CI: 1.01–1.32) as reviewed by Quach et al. [20] from a single meta-analysis [93]. Iqbal et al. [96] identified three meta-analyses on residential pesticide exposure and offspring cCNSt and one meta-analysis on parental occupational exposure in their systematic review. There was an elevated risk with residential exposure to pesticides but only two studies had significant estimates (OR range: 1.11–1.35; most precise OR: 1.26, 95% CI: 1.10–1.45) [93, 97, 98], and one [99] had a null finding with parental occupational exposure during childhood. Buser et al. [53] identified two studies in which exposure to crops, a proxy for pesticide exposure, was associated with cCNSt risk (OR: 1.22, 95% CI: 1.15–1.29) [100] and the other reported higher urinary levels of pyrethroids in children with cCNSt [101] (4th vs 1st quartile OR: 3.60, 95% CI: 1.87–6.93) [53]. Finally, we identified two additional meta-analyses that reported significant risk with childhood exposure to pesticides and cCNSt (OR range: 1.31–1.34, most precise OR: 1.34, 95% CI: 1.15–1.56) [23, 95]. In summary, there is evidence that exposure to pesticides may increase risk of cCNSt, but the exposure mechanism, specific chemical(s), and susceptibility window is inconclusive.

Farm Residence and Exposures

In addition to pesticide exposures, living on a farm can expose parents and children to zoonotic viruses, bacteria, endotoxins, inorganic dust, and chemicals from fertilizers [102]. These exposures could be associated with risk of cCNSt if exposures to viruses and bacteria induces a stronger immune response or can increase risk if exposures cause DNA damage [102, 103]. Zumel-Marne et al. summarized the literature on living on a farm and/or with farm animals and cCNSt risk and reported an elevated risk of cCNSt for offspring (OR: 1.17, 95% CI: 0.69–1.98) of mothers who lived on a farm during pregnancy [23]. Zumel-Marne et al. [23] found three studies reporting elevated risk of cCNSt with mothers' contact with animals during pregnancy (OR range: 1.4–5.1; most precise OR: 1.4, 95% CI: 1.0–1.9) [104–106]. Zumel-Marne et al. [23] also meta-analyzed studies of living on a farm during childhood and cCNSt (OR: 1.28, 95% CI: 0.98–1.68). Because living on a farm is linked to several exposures the literature on living on a farm and risk of cCNSt is inconclusive.

Parental Occupation

Occupational exposures may impact DNA and epigenetics in sperm [107] or various molecular mechanism in the developing fetuses [52]. Zumel-Marne et al. [23] reviewed 14 studies encompassing a range of parental occupations such as agricultural farming, aerospace activities, and health services in association with cCNSt. Studies differed by occupations included, how exposure was assessed, timing of exposure (i.e., before conception, during pregnancy, childhood), and parent. Because some studies have already been included in the meta-analyses we have discussed herein (e.g., parental occupation to pesticides), we refer readers to the Zumel-Marne et al. [23] article for more details. Overall, findings for parental occupational exposure and cCNSt are inconclusive due variation across studies.

Discussion

While cCNSt are the most common solid malignancies diagnosed in children, there is limited evidence about their etiology beyond genetic predisposition and radiation exposure, which we reported on herein. Other endogenous and exogenous factors that increase cCNSt risk included, increasing maternal age, race/ethnicity, maternal meat intake during pregnancy, increasing sibship size (may be associated with maternal age), high and very low birth weight, paternal smoking and maternal passive smoke exposure during pregnancy, childhood ionizing radiation exposure, pesticide exposure (parental and childhood). Conversely, factors with strong evidence for reducing risk of cCNSt included folic acid supplementation during pregnancy, increasing birth order of the child, and the presence of allergic conditions during childhood. Conflicting reports were present for parental education, seasonality of birth, tap water contamination, air pollution, radon, and living on a farm.

Our umbrella review identified some limitations of the individual studies. First, cCNSt are highly heterogeneous in terms of their histological and molecular subtypes. Several individual studies performed analyses by histological subtypes, when possible, but this approach is largely lacking due to sample size challenges and lack of data. As molecular subtypes are relatively recent categorizations, none of the publications reported associations by molecular subtypes. In order to understand the etiology of cCNSt, the field must evolve to consider such heterogeneity by not only histology, but molecular subtypes [108, 109]. As molecular subtypes are being used in the clinic for diagnosis and treatment, we strongly encourage such information be recorded by state cancer registries enabling researchers to assess this information in their registry linkage studies of prenatal and demographic characteristics for cCNSt.

Second, exposure assessment methods in some of these studies were limited to linking residential addresses to area-based exposure estimates, using data collected from registries, or asking parents to recall exposures. Novel molecular methods to assess exposures (e.g., metabolomics, DNA methylation risk scores) are available to objectively measure prenatal and childhood exposures in matrices like primary teeth and newborn dried blood spots [110]. Further, linking risk factor information for exposures outlined herein to somatic mutational signatures in human cancers [69] may allow us to use not only survey or registry data but somatic data to understand etiologic heterogeneity. Third, cCNSt is more common in males than females. Environmental risk factors may vary by sex and should be investigated in stratified analyses.

Future directions of research into risk factors for cCNSt should encompass both genomic and novel exposure assessment methods. Studies without molecular subtype information contribute to only incremental in progress in prevention. This review highlights some intervenable pathways to reduce cCNSt risk such as maternal pregnancy folic acid supplementation, pesticide use reduction, and limited use of radiation in medical settings. While histologic and molecular diversity of cCNSt creates logistical challenges in conducting properly powered studies into etiologic heterogeneity, large consortia of researchers from around the world remain crucial in removing these barriers and moving us toward better epidemiologic knowledge of cCNSt risk factors and ultimately prevention.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

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