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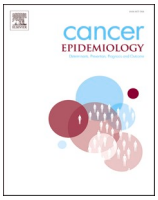

Risk factors for childhood brain tumours: A systematic review and meta-analysis of observational studies from 1976 to 2022

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ABSTRACT

Background: Childhood brain tumours (CBTs) are the leading cause of cancer death in children under the age of 20 years globally. Though the aetiology of CBT remains poorly understood, it is thought to be multifactorial. We aimed to synthesize potential risk factors for CBT to inform primary prevention.

Methods: We conducted a systematic review and meta-analysis of epidemiological studies indexed in the PubMed, Web of Science, and Embase databases from the start of those resources through 27 July 2023. We included data from case-control or cohort studies that reported effect estimates for each risk factor around the time of conception, during pregnancy and/or during post-natal period. Random effects meta-analysis was used to estimate summary effect sizes (ES) and 95% confidence intervals (CIs). We also quantified heterogeneity (I^2) across studies.

Findings: A total of 4040 studies were identified, of which 181 studies (85 case-control and 96 cohort studies) met our criteria for inclusion. Of all eligible studies, 50% (n = 91) were conducted in Europe, 32% (n = 57) in North America, 9% (n = 16) in Australia, 8% (n = 15) in Asia, 1% (n = 2) in South America, and none in Africa. We found associations for some modifiable risk factors including childhood domestic exposures to insecticides (ES 1.44, 95% CI 1.20–1.73) and herbicides (ES 2.38, 95% CI 1.31–4.33). Maternal domestic exposure to insecticides (ES 1.45, 95% CI 1.09–1.94), maternal consumption of cured meat (ES 1.51, 95% CI 1.05–2.17) and coffee ≥ 2 cups/day (ES 1.45, 95% 95% CI 1.07–1.95) during pregnancy, and maternal exposure to benzene (ES 2.22; 95% CI 1.01–4.88) before conception were associated with CBTs in case-control studies. Also, paternal occupational exposure to pesticides (ES 1.48, 95% CI 1.23–1.77) and benzene (ES 1.74, 95% CI 1.10–2.76) before conception and during pregnancy were associated in case-control studies and in combined analysis. On the other hand, assisted reproductive technology (ART) (ES 1.32, 95% CI 1.05–1.67), caesarean section (CS) (ES 1.12, 95% CI 1.01–1.25), paternal occupational exposure to paint before conception (ES 1.56, 95% CI 1.02–2.40) and maternal smoking > 10 cigarettes per day during pregnancy (ES 1.18, 95% CI 1.00–1.40) were associated with CBT in cohort studies. Maternal intake of vitamins and folic acid during pregnancy was inversely associated in cohort studies. Hormonal/infertility treatment, breastfeeding, child day-care attendance, maternal exposure to electric heated waterbed, tea and alcohol consumption during pregnancy were among those not associated with CBT in both case-control and cohort studies.

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Conclusion: Our results should be interpreted with caution, especially as most associations between risk factors and CBT were discordant between cohort and case-control studies. At present, it is premature for any CBT to define specific primary prevention guidelines.

1. Introduction

Childhood brain tumours (CBTs) are a heterogeneous group of solid tumours and the leading cause of cancer death in children under the age of 20 years. [1] CBT accounts for one quarter of all paediatric cancers [2], global cancer registry data suggest that incidence and mortality are higher in high-income countries (HIC) than low- and middle-income countries (LMIC) [3]. However, incidence of low-income countries (LIC) is usually underestimated for several reasons including limited access to health system, insufficient availability of imaging and treatments, lack of population registries [4]. Even in HIC, complete ascertainment poses challenges, as some cases are only seen in neurosurgery and some adolescents are seen in adult clinics. According to international rules, cancer registries have to include in CBT all intracranial tumours, malignant or not (except for intracranial germ cell tumours, categorized in the group of germ cell tumours). However, registration of non-malignant tumours is heterogeneous between registries [5,6]. Hence, for CBT, how much of the observed geographical differences are attributable to true underlying incidence differences and remains unknown. This under-ascertainment has recently been confirmed in studies investigating the effects of the Covid19 pandemic on occurrence of childhood cancer incidence, where one proposed consequence was that more CBT patients were seen in paediatric oncology compared to adult neurosurgery as the latter were more affected by the pandemic, see for instance Germany [7].

CBT groups several entities, themselves heterogeneous in terms of histology, topology, malignancy, grade and molecular profiles [8]. The International Classification of Childhood Cancers (ICCC3) splits the group III of central nervous system (CNS) tumours into five subgroups, ependymomas and tumours of the plexus choroid (7%), astrocytomas (41%), the most frequent subgroup with a majority of pilocytic astrocytomas (grade 1), embryonal tumours (17%), of which the majority are medulloblastomas, gliomas other than astrocytomas (“other gliomas”, 10%), rarer subtypes grouped into "other CNS tumours" (20%) and unspecified tumours (5%) [9–11]. Since 2016, the CBT classification has evolved substantially, and differentiates new entities on the basis of genomic and epigenetic alterations in addition to the morphology and topology criteria [12].

The aetiology of CBT remains poorly understood, it is suggested to result from cellular genetic alterations of normal regulatory mechanisms [13–15]. Several factors including genetic predispositions, birth and parental characteristics, environmental and parental occupational exposures have been hypothesized as potential risk factors. However, the results remain inconsistent and inconclusive for most risk factors [16–25].

The present study aimed at synthesizing potential risk factors for CBT geared towards modifiable risk factors to inform primary prevention of the disease, adding to previous review studies [26–30] on the time span and geographical coverage.

2. Materials and methods

This study was conducted in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) check list of 2020 [31] (appendix pp 3–5).

2.1. Search strategy and eligibility criteria

We searched PubMed, Web of Science, and Embase databases for articles without restriction on publication date and language and extracted information from original articles published in peer-reviewed journals from 1976 to 2022. The studies were included if they 1) were case-control or cohort studies, 2) reported effect estimates for specific exposure time window: preconception, prenatal or postnatal, and 3) reported risks of CBT for children below 20 years old at diagnosis. Only studies that provided estimates of the Relative Risk (RR), such as Odds Ratio (OR), Hazard Ratio (HR), Standardized Mortality Ratio (SMR), Mortality Rate Ratio (MRR), Standard Incidence Ratio (SIR) or Incidence Rate Ratio (IRR) with 95% confidence intervals (CIs) were included. When multiple studies were identified from the same cohort/authors, we included them if they reported results that were not overlapping, e.g., either for different risk factors or for different time windows of exposure periods. If they studied the same risk factors in the same geographical location and for the same exposure time windows, only the most recent results with the longest follow-up or the largest study population was included. We also excluded published pooled analyses, criteria for inclusion and exclusion were defined a priori.

2.2. Information sources

Peer reviewed scientific articles were identified and retrieved through PubMed, Web of Science (WOS) and Embase databases, imported and automatically screened for duplicates in EndNote version X9.3.3, and subsequently screened manually. We retrieved additional relevant scientific articles that met the inclusion criteria, identified through the exploration of lists of references (snowballing). The initial search was performed in June 2022 and updated until July 2023.

2.3. Search strategy

The research question was formatted according to the PECO statement (Population, Exposure, Comparison and Outcome) and in line with the PRISMA check list of 2020 [31,32]. The search strategy included a list of key words and MeSH terms with filters (appendix pp 2–13).

2.4. Selection process

The first (FMO) and second (RD) authors independently assessed the titles, abstracts, and full text of the articles according to the a priori defined inclusion criteria for eligibility and study protocol. Discrepancies following the independent selection process were resolved by consensus in line with the Cochrane handbook for systematic reviews.

2.5. Data collection process

Following removal of duplicates and screening, we extracted the following data from the full-text articles: authors’ name, year of publication, study location (city, country and continent), period of diagnosis, age range at diagnosis, exposures, exposure assessment methods, outcome ascertainment, number of CBT or, if not available, of childhood cancer cases and controls/study population, follow-up duration, as well as risk estimates with their respective CIs. Information on study design (case-control and cohort or nested case-control) was also extracted. Registry-based case-control studies (with exposure data from censuses, hospital records, and other register data) and Nested case-control studies were considered as cohort studies.

Among exposures extracted were birth and parental characteristics, pesticides and other chemicals, radiation, and lifestyle factors. CBT subtypes were reported according to the recent International Classification of Childhood Cancer (ICCC-3) [11]. In the meta-analysis, the term

embryonal tumours was used for all embryonal tumours, only PNET, or only medulloblastoma depending on the original work. Paediatric spinal cord tumours are extremely rare (0.27 per 100,000.00 children), some authors combined them with brain tumours and reported as CNS tumours. Thus, we classified all tumours in the present study as CBT [33].

Only few studies [34–37] reported risk estimate of parental education as the majority of authors merely adjusted for it. Hence, we did not report parental education due to obvious publication bias.

2.6. Quality assessment of eligible articles

Included articles were subjected to a rigorous appraisal (by FMO) for methodological quality using Joanna Briggs Institute critical appraisal (JBI) tools for case-control and cohort studies [38]. The critical appraisal checklist has 10 criteria for case-control and 11 for cohort studies. Each question with "yes" score 1, "no" score 0 and "unclear" or "not applicable" score 0 (appendix pp 14–19).

2.7. Statistical analyses

We computed and reported pooled effect sizes (ES) with their respective 95% CIs using random-effects meta-analyses [39]. Case-control studies including direct contact with the study participants were first analysed separately to cohort-, registry-based and nested case-control studies and secondly in combined case-control-cohort analysis. The reason was that biases operate differently in direct (information from participants) vs. indirect data (information extracted from registries without involving the participants) collection, insofar that recall bias common in case-controls studies mostly leads to bias away from the null effect while measurement error independent of disease status mostly leads to bias towards the null effect. To investigate potential publication bias, funnel plots and Egger's test were used [40]. The I^2 statistic was assessed to quantify the heterogeneity of the results between studies. I^2 values of 0% were considered to represent "no heterogeneity", from 1% to 35% "low heterogeneity", from 36% to 55% as "moderate", from 56% to 70% as "substantial" and above 71% as "considerable" heterogeneity [41]. As standard requirement, a minimum of 2 studies were needed for the meta-analysis and 3 studies for the bias analysis. Furthermore, we also performed sensitivity analyses by stratifying the studies by: 1) publication year to explore any time trend and 2) geographical region where the studies were conducted. A nominal significance level of 0.05 was used for heterogeneity and Egger's tests. Analyses were conducted using STATA® software, version 15.1 (College Station, TX, USA).

2.8. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

3. Results

3.1. Search strategy outcome

Our search strategy yielded a total of 4040 studies, whereof 196 articles were duplicates. Further 3344 non-eligible articles were removed based on titles and abstracts. Five hundred articles underwent full-text assessment for eligibility, of which 319 were excluded for various reasons (Fig. 1). In total, 181 articles (85 case-control and 96 cohort studies including nested / registry-based case-control studies) were included in the systematic review and meta-analysis (Table 1 and Fig. 1).

3.2. Study characteristics

Of all eligible studies, 50% (n = 91) were conducted in Europe, 32% (n = 57) in North America, 9% (n = 16) in Australia, 8% (n = 15) in Asia, and 1% (n = 2) in South America. There was no study from Africa.

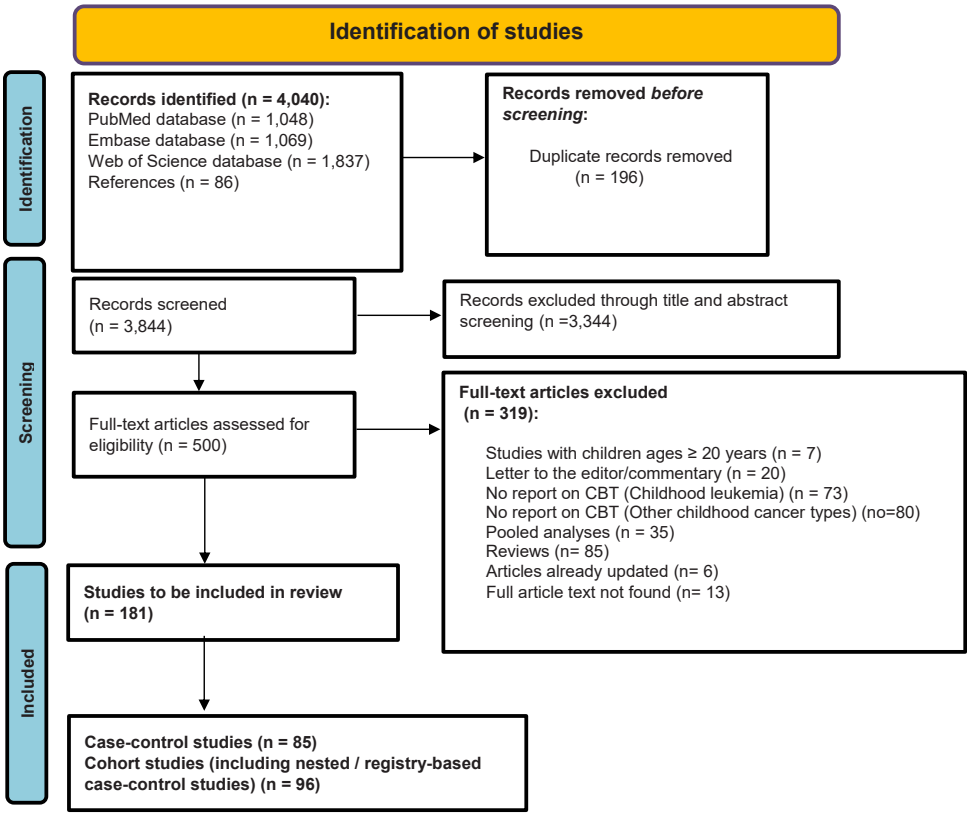

Fig. 1. PRISMA flowchart of articles included in this systematic review and meta-analysis of risk factors for CBT.

Table 1
Characteristics of studies included in the systematic review and meta-analysis, sorted by geographical region.

Case-control studies								
First author	**Country**	**Date of diagnoses**	**Age (years)**	**Risk factor**	**Exposure assessment**	**Outcome ascertainment**	**†Cases**	**Control**
	Asia							
Chen et al., 2016[22]	China - Eastern	2012–2015	< 15	Postnatal exposure to pyrethroids pesticides	Face-to-face interview + urine collection	Cancer registry	161	170
Shu et al.,1994 [42]	China - Shanghai	1981–1991	< 15	Diagnostic X-ray and ultrasound in multiple exposure window	Face-to-face interview	Cancer registry	107	107
Ji et al. 1997 [43]	China - Shanghai	1981–1991	< 15	Paternal smoking during preconception and postnatal periods	Face-to-face interview	Cancer registry	107	107
Hu et al., 2000 [35]	China- Northeast	1991–1996	< 19	Parental smoking preconception and prenatal period	Face-to-face interview	Hospital records	82	246
Saito et al., 2010[44]	Japan	199–2002	< 15	Postnatal exposure to power-Frequency Magnetic Fields	Measurements and interview	Hospital records	55	99
Smulevich et al., 1999 [45]	Russia - Moscow	1986–1988	< 15	Multiple risk factors during preconception and prenatal exposure	Face-to-face interview	Cancer registry	57	1181
	Australia /Oceania							
Mccredie et al., 1994a [46]	Australia- New South Wales	1985–1989	< 15	Perinatal risk-factors	Face-to-face interview	Cancer registry	82	164
Mccredie et al., 1994b [47]	Australia- New South Wales	1985–1989	< 15	Perinatal and early postnatal risk factors	Face-to-face interview	Cancer registry	82	164
Milne et al., 2012[48]	Australia	2005–2010	< 15	Maternal prenatal use of folic acid	Mailed questionnaires	Paediatric oncology centres	327	867
Greenop et al., 2013[49]	Australia	2005–2010	< 15	Pesticide (Multiple exposures window)	Self-administered questionnaire and telephone interview	Paediatric oncology centres	303	941
Milne et al., 2013a[50]	Australia	2005–2010	< 15	Parental alcohol consumption (preconception and prenatal exposures)	Self-administered questionnaire	Paediatric oncology centres	549	1742
Milne et al., 2013b[51]	Australia	2005–2010	< 15	Parental smoking (preconception and prenatal exposures)	Self-administered questionnaire	Paediatric oncology centres	302	1742
Peters et al., 2013[52]	Australia	2005–2010	< 15	Parental occupational exposure to engine exhausts	Self-administered questionnaire and telephone interview	Paediatric oncology centres	306	950
Greenop et al., 2014a[53]	Australia	2005–2010	< 15	Perinatal risk factors	Self-administered questionnaire	Paediatric oncology centres	319	1079
Greenop et al., 2014b[54]	Australia	2005–2010	< 15	Maternal prenatal consumption of coffee and tea	Self-administered food frequency questionnaire	Paediatric oncology centres	293	726
Greenop et al., 2014c[55]	Australia	2005–2010	< 15	Parental occupational painting and floor treatments	Self-administered questionnaire	Paediatric oncology centres	306	950
Milne et al., 2014[56]	Australia	2005–2010	< 15	Postnatal and parental diagnostic radiological procedures	Self-administered questionnaire	Paediatric oncology centres	319	1079
Peters et al., 2014[57]	Australia	2005–2010	< 15	Parental occupational exposure to solvents	Self-administered questionnaire and telephone interview	Paediatric oncology centres	306	950
Dockerty et al., 1998[58]	New Zealand	1990–1993	< 15	Parental occupational exposure to electromagnetic field (EMF)	Face-to-face interview	Cancer registry	58	303
Greenop et al., 2015[59]	Australia	2005–2010	< 15	Breast feeding	Self-administered questionnaire	Paediatric oncology centres	299	733
	Europe							

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Table 1 (*continued*)

Andersen et al., 2013 [60]	Denmark, Norway, Sweden and Switzerland	2004–2008	7–19	Postnatal exposure to infectious diseases	Face-to-face interview	Hospitals and cancer registries	352	646
Tettamanti et al., 2017 [61]	Denmark, Norway, Sweden and Switzerland	2004–2008	7–19	Prenatal and postnatal medical conditions	Face-to-face interview	Cancer registry	352	646
Christensen et al., 2012 [62]	Denmark, Norway, Sweden, and Switzerland	2004–2008	7–19	Prenatal and postnatal exposure to animals and farm life	Face-to-face interview	Cancer registries	352	646
Vienneau et al., 2016 [63]	Denmark, Sweden, Norway and Switzerland	2004–2008	7–19	Perinatal risk factors	Face-to-face interview	Cancer registry	352	646
Cordier et al., 1994[34]	France	1985–1987	< 16	Multiple risk factors during prenatal and postnatal periods	Face-to-face interview	Hospital records	75	113
Mallol-Mesnard et al. 2008 [64]	France	2003–2004	< 15	Perinatal risk factors	Telephone interview	Cancer registry	209	1681
Plichart et al., 2008[65]	France	2003–2004	< 15	Parental smoking, maternal alcohol, coffee and tea consumption during preconception and prenatal periods	Telephone interview	Cancer registry	209	1681
Schüz et al. and Forman, 2007[66]	Germany	1992–1994	< 15	Perinatal risk factors	Self-administered questionnaire and telephone interview	Cancer registry	389	2024
Schüz et al., 2007[67]	Germany	1992–1997	< 15	Maternal medication use during prenatal period	Self-administered questionnaire and telephone interview	Cancer registry	399	2057
Spix et al., 2009[68]	Germany	1993–2003	< 5	Multiple risk factors during prenatal and postnatal periods	Telephone interviews	Cancer registry	102	246
Hug et al., 2010[69]	Germany	1992–1997	< 15	Parental occupational exposures to EMF	Self-administered questionnaire and telephone interview	Cancer registry	444	2382
Schüz et al., 1999[70]	Germany	1992–1994	< 15	Multiple risk factors during preconception and prenatal periods	Self-administered questionnaire and telephone interview	Cancer registry	399	2588
Schüz et al., 2001[30]	Germany	1988–1994	< 15	Multiple risk factors during multiple window periods	Self-administered questionnaire and telephone interview	Cancer registry	466	2458
Georgakis, et al. 2019 [71]	Greece	2010–2016	< 15	Multiple risk factors during multiple window periods	Face-to-face and telephone interview	Cancer registry	203	406
Filippini et al., 2000[72]	Italy- Lombardy	1988–1993	< 16	Parental smoking during prenatal period	Telephone interview	Hospital records	244	502
Filippini et al., 1994[36]	Italy- Milan, Varese and Como	1985–1988	< 16	Maternal smoking during prenatal period	Face-to-face interview	Hospital records and cancer registry	91	321
Pavlovic et al., 2005[37]	Serbia	1998–2000	< 20	Multiple risk factors during prenatal period	Face-to-face interview	Hospital records	60	60
Ortega-García et al., 2010 [73]	Spain	2004–2006	< 15	Periconceptional folic acid intake	Telephone interview	Hospital records	222	155
Sorahan et al., 1997[74]	UK	1953–1955	< 16	Parental smoking during preconceptional and prenatal	Face-to-face interview	Birth registry	229	229
Pang et al., 2003[75]	UK	1991–1994	< 15	Parental smoking during preconceptional postnatal	Face-to-face interview	Cancer registry	635	6987
Harding et al., 2009[76]	UK	1992–1994	< 15	Postnatal exposure to infection	Face-to-face interview	Cancer registry	576	6276
Smith et al., 2009[77]	UK - England and Wales	1991–1996	< 15	Perinatal risk factors	Face-to-face interview	Cancer registry	702	6337

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Table 1 (*continued*)

Rajaraman et al., 2011 [78]	UK -England and Wales	1992–1996	< 15	Diagnostic radiation during prenatal and postnatal periods	Face-to-face interview	Histopathology review database or individual consultant	482	4857
UKCCS, 1999 [79]	UK -England and Wales	1991–1995	< 15	Postnatal exposure to EMF	Face-to-face interview	Health records	387	798
Sorahan et al., 1999[80]	UK- Oxford	1953–1981	< 16	Parental occupational exposures to EMF during preconceptional, prenatal and postnatal periods	Face-to-face interview	Hospital records	362	334
McKinney et al., 1999 [81]	UK –Scotland	1991–1994	< 15	Multiple risk factors during different window periods	Face-to-face interview	Cancer registry	75	133
Harding et al., 2007[82]	UK- -Scotland, England, and Wales.	1991–1996	< 15	Breast feeding	Face-to-face interview	Hospital records	686	7621
McKinney et al., 2003 [83]	UK- -Scotland, England and Wales.	1991–1996	< 15	Multiple parental occupation exposures	Face-to-face interview	Hospital records	[a]3838	7629
	North America							
Howe et al., 1989[84]	Canada-Toronto	1977–1983	< 20	Multiple risk factors during different window periods	Face-to-face interview	Hospital records	74	138
Khan et al., 2010[85]	USA	1991–1997	< 6	Postnatal diagnostic X-rays	Telephone interview	Children's Oncology Group	299	299
Tran et al., 2017[18]	USA	1957–1991	< 15	Perinatal risk factors	Comprehensive Epidemiologic Data Resource (CEDR)	Hospital records	72	822
Barrington-Trimis et al., 2013[86]	USA - Los Angeles, San Francisco, and Seattle regions	1984–1991	< 11	Parental smoking during prenatal period	Face-to-face interview	SEER registries	202	286
Bunin et al., 1994[87]	USA and Canada	1968–1989	< 6	Multiple risk factors during different exposure periods	Face-to-face interview	Children's cancer group	321	321
Van Wijngaarden et al., 2003 [88]	USA and Canada	1986–1989	< 6	Parental occupational exposure to pesticides	Telephone interview	Children's cancer group	322	321
Bunin et al., 2005[89]	USA and Canada	1991–1997	< 6	Maternal overall diet during prenatal period	Telephone interview	Children's cancer group	315	315
Bunin et al., 2006a[90]	USA and Canada	1991–1997	< 6	Maternal supplement during prenatal period	Telephone interview	Children's cancer group	315	315
Bunin et al., 2006b[91]	USA and Canada	1991–1997	< 6	Parental heat exposure during pregnancy	Telephone interview	Children's cancer group	318	318
Rosso et al., 2008[23]	USA and Canada	1991–1997	< 7	preconceptional an prenatal exposure to painting	Telephone interview	Cancer registry	318	318
John et al., 1991[92]	USA- Colorado	1976–1983	< 15	Prenatal exposure to smoking	Face-to-face and telephone interview	Cancer registry	48	196
Feingold et al., 1992[93]	USA- Colorado	1976–1983	< 15	Parental occupational exposure to chemicals	Face-to-face and telephone interview	Cancer registry	31	222
Sarasua and Savitz, 1994 [94]	USA- Colorado	1976–1984	< 15	Parental occupational exposure to chemicals	Face-to-face and telephone interview	Cancer registry	45	206
Wilkins and Wellage, 1996[95]	USA- Columbus	1975–1982	< 20	Parental occupational exposure to EMF	Telephone interview	Hospital records	94	166
Davis et al., 1993[96]	USA- Missouri	1985–1989	< 11	Pesticides exposure during multiple exposure windows	Telephone interview	Cancer registry	45	193
Kuijten et al., 1990[97]	USA- Pennsylvania, New Jersey, and Delaware	1980–1986	< 15	perinatal risk factors	Telephone interview	Hospital records	163	163
Kuijten et al., 1992[98]	USA- Pennsylvania, New	1980–1986	< 15	Multiple parental occupational exposures	Face-to-face and telephone interview	Cancer registry	321	313

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Table 1 (*continued*)

	Jersey, and Delaware							
Shim et al., 2009[99]	USA- Pennsylvania, New York, and Florida	1993–1997	< 10	Pesticides exposure during preconceptional and prenatal periods	Telephone interviews	Cancer registry	526	526
Mueller et al., 2001[100]	USA- Seattle San Francisco, California, and western Washington State, Seattle-Puget Sound area	1984–1990	< 20	Multiple lifestyle risk factors during prenatal periods	Face-to-face interview	Cancer registry	540	801
Norman et al., 1996[101]	USA- West Coast	1984–1991	< 20	Parental smoking during preconceptional and prenatal periods	Face-to-face and telephone interview	Cancer registry and SEER	540	801
Holly et al., 1998[102]	USA- West Coast	1984–1991	< 20	Farm and animal exposures during preconceptional and prenatal periods	Face-to-face interview	Cancer registry	540	801
McKean-Cowdin et al., 1998 [103]	USA- West Coast	1984–1991	< 20	Multiple parental occupation exposures during preconceptional and prenatal periods	Face-to-face interview	Cancer registry	540	801
Gold et al., 1993[104]	USA-California	1977–1981	< 18	Parental smoking during preconceptional and prenatal period	Face-to-face interview	SEER registry	361	1083
Preston-Martin et al., 1996[105]	USA-California	1984–1991	< 20	Postnatal exposure to EMF	EMF measurement	NA	298	298
Pogoda and Preston-Martin, 1997[106]	USA-California	1984–1991	< 20	Domestic pesticides exposure during prenatal and postnatal periods	Telephone interview	NA	224	218
Yeazel et al., 1997[107]	USA-California	1982–1989	< 18	Perinatal risk factors	Self-administered questionnaire	Children's Cancer Group (CCG)	252	816
Davis et al., 1988[108]	USA-Colorado	1976–1983	< 16	Breast feeding	Face-to-face interview	Cancer registry	251	222
Savitz et al., 1990[109]	USA-Colorado	1976–1983	< 15	Prenatal exposures to electric appliances	Face-to-face and telephone interview	Cancer registry	252	222
Savitz et al., 1993[110]	USA-Colorado	1976–1983	< 15	Postnatal exposure to residential wire code	Face-to-face and telephone interview	Cancer registry	67	260
Savitz and Ananth, 1994[111]	USA-Colorado	1976–1983	< 15	Perinatal risk factors	Face-to-face and telephone interview	Cancer registry	47	212
Leiss and Savitz, 1995 [112]	USA-Colorado	1970–1976	< 15	Prenatal and postnatal exposure to domestic pesticide	Face-to-face and telephone interview	Cancer registry	252	222
Savitz et al., 1988[113]	USA-Colorado	1976–1983	< 15	Postnatal exposure to magnetic fields	Face-to-face and telephone interview	Cancer registry	67	48
Savitz and Feingold, 1989[114]	USA-Colorado	1976–1983	< 15	Postnatal exposure to traffic density	Face-to-face and telephone interview	Cancer registry	67	262
Wilkins and Sinks, 1990 [115]	USA-Ohio	1975–1982	< 20	Parental occupational exposure EMF	Face-to-face and telephone interview	Cancer registry	110	193
Nasca et al., 1988[116]	USA-New York	1968–1977	< 15	Parental occupational exposure to chemicals and radiation	Face-to-face interview	Cancer registry	338	676
Gurney et al., 1996[117]	USA-Seattle and Washington	1984–1990	< 20	Postnatal exposure to power line configurations, electric heating sources, and electric appliance	Face-to-face interview	Cancer registry and SEER	133	270
	South America							
Rios et al., 2018[118]	Peru	2012–2015	< 18	Parental characteristics	Self-administered questionnaire and Hospital records	Hospital records	62	124

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Table 1 (*continued*)

Cohort studies (including nested / registry-based case-control studies)									
First author	**Country**	**Date of diagnoses**	**Age (years)**	**Risk factor**	**Exposure assessment**	**Outcome ascertainment**	**Cases**	**Study Population/ control**	**Follow up (Years)**
	Asia								
Huang et al., 2014[119]	China-Taiwan	1998–2006	< 18	Postnatal exposure to head CT	National health insurance research database records	Catastrophic illness certificate database (CICD) and histologically or cytologically	49	24,418	2
Heck et al., 2020[120]	China-Taiwan	2004–2014	< 12	Gestational risk factors	Hospital records	Cancer registry	260	2079,037	12
Weng et al., 2022[121]	China-Taiwan	2004–2017	< 14	Assisted reproductive technology (ART)	National databases	Cancer registry	328	2, 308,016	11
Kessous et al., 2019[122]	Israel	1991–2014	< 19	Smoking during pregnancy	Hospital records	Cancer registry	38	238,432	18
Kessous et al., 2020a[123]	Israel	1991–2014	< 19	Gestational age	Hospital records	Cancer registry	35	231344	18
Kessous et al., 2020b[124]	Israel	1991–2014	< 19	Maternal pre-pregnancy obesity	Hospital records	Cancer registry	38	238 005	11
Cha et al., 2011[125]	Korea	1995–2006	< 12	Birth characteristics	Birth database	Death database	344	6479,406	11
Hong et al., 2019[126]	South Korea	2006–2015	< 20	Postnatal exposure to diagnostic low-dose ionizing radiation	National health insurance system	National Health Insurance System	2872	12 068 821	19
	Australia /Oceania								
Stavrou et al., 2009[127]	Australia- New South Wales	1994–2005	< 13	Maternal smoking during pregnancy	Midwives data collection	Cancer registry	20	979,809	12
Mathews et al., 2013[128]	Australia	1985–2005	< 20	Postnatal exposure to computed tomography (CT) scans	Health services records	Cancer registry	283	10.9 million	10
	Europe								
Yeh et al., 2022[129]	Denmark	1978–2016	< 20	Birth characteristics	Birth records	Cancer registry	1678	39,256	19
Olsen et al., 1993[130]	Denmark	1968–1986	< 15	Postnatal residential exposure to high voltage facilities	Generated field levels	Cancer registry	624	1872	14
Mellemkjær et al., 2006 [131]	Denmark	1977–1989	< 20	Birth characteristics	Hospital records	Cancer registry	25	50	19
Pedersen et al., 2015[132]	Denmark	1968–2003	< 15	Postnatal exposure to extremely low-frequency magnetic fields (ELF-MF)	Calculated strength of ELF-MF at addresses within distance criteria	Cancer registry	624	1872	14
Contreras et al., 2017 [21]	Denmark	1968–2015	< 16	Parental characteristics	Birth certificates	Cancer registry	1548	585,594	15
Raaschou-Nielsen et al., 2018 [133]	Denmark	1968–1991	< 15	Postnatal exposure to ambient benzene	Residential addresses from registries	Cancer registry	233	5428	14
Erdmann et al., 2020 [134]	Denmark	1981–2013	< 20	Parental socioeconomic differences	Geodata and socioeconomic records	Cancer registry	1273	5086	19
Hall et al., 2020[135]	Denmark	1968–2016	< 17	Parental occupational livestock or animal dust	Birth registry and parental occupational history	Cancer registry	125	6393	16
Volk et al., 2019a[136]	Denmark	1968–2015	< 20	Parental occupational painting exposure	Employment history and job exposure matrix	Cancer registry	1111	22220	19
Volk et al., 2019b[137]	Denmark	1968–2016	< 20	Parental occupational exposure to diesel engine exhaust	Employment history and job exposure matrix	Cancer registry	1141	28,525	19
Volk et al., 2020[138]	Denmark	1968–2016	< 20	Parental occupational organic dust exposure	Employment history and job exposure matrix	Cancer registry	1929	46844	19
Raaschou-Nielsen et al., 2001 [139]	Denmark	1968–1991	< 15	Postnatal exposure to air pollution	Residential history	Cancer registry	740	2220	14
Momen et al., 2016[140]	Denmark	1996–2008	< 15	Maternal smoking during pregnancy	National patient register	Cancer registry	128	888,556	14

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Table 1 (*continued*)

Schüz et al., 2015	Denmark	1973–2010	< 20	Birth characteristics	Population and birth registers	Cancer registry	1469	2461,283	20
Patel et al., 2020[141]	Denmark	1996–2003	< 15	Residential proximity to agriculture	Geocoded household addresses	Cancer registry	59	9394	14
Hvidtfeldt et al., 2020 [142]	Denmark	1981–2013	< 20	Postnatal exposure to Nitrogen Dioxide (NO2)	National administrative registries	Cancer registry	1275	4596	19
Momen et al., 2014[143]	Denmark, Finland and Sweden	1973–2007	< 15	Caesarean section (CS)	Birth registers	Cancer registries	2779	882 907	14
Schmidt et al. 2010a[17]	Denmark, Finland, Sweden, and Norway	1985–2006	< 15	Perinatal risk factors	Childcare database records	Cancer registry and Nordic Society of Paediatric Haematology and Oncology	3426	16,039	14
Schmidt et al. 2010b[144]	Denmark, Finland, Sweden, and Norway	1985–2006	< 15	Postnatal exposure to infections	Childcare database records	Cancer registry and Nordic Society of Paediatric Haematology and Oncology	3600	17 848	14
Bjørge et al., 2013[16]	Denmark, Finland, Norway, and Sweden	1967–2010	< 15	Perinatal risk factors	Face-to-face interview	Cancer registries and in direct reports from pediatric, oncology, and neurosurgery hospitals	5163	172 422	14
Sundh et al., 2014[145]	Denmark, Finland, Sweden and Norway	1982–2012	< 20	ART	Birth registers	Cancer registries	156	450,215	19
Hakulinen et al., 1976 [146]	Finland	1965–1970	< 15	Parental occupational exposure to hydrocarbons	Antenatal records	Cancer registry	219	219	14
Seppälä et al., 2020[147]	Finland	1996–2014	< 20	Gestational diabetes	Birth registry	Cancer registry	484	2407	19
Verkasalo et al., 1993 [148]	Finland	1970–1989	0–19	Postnatal exposure to power lines	Calculated magnetic fields	Cancer registry	39	134 800	17
Foucault et al., 2022[149]	France	2000–2011	< 18	Childhood CT scans	Radiological records	Cancer registry	75	100,560	17
Hammer et al., 2010[150]	Germany	1976–2003	< 15	Postnatal exposure to diagnostic X-Ray	Radiation dose measurement	Cancer registry	10	92957	8
Krille et al., 2015[151]	Germany	1980–2010	< 15	Postnatal exposure to ionising radiation from CT	Radiology information systems (RIS) record	Cancer registry	8	44,584	14
Meulepas et al., 2019 [152]	Netherlands	1979–2012	< 19	Postal exposure to CT scans	Hospital records	Cancer registry	84	168394	18
Tynes and Haldorsen, 1997[153]	Norway	1965–1989	< 15	Postnatal exposure to magnetic fields	EMF measurement	Cancer registry	156	2004	14
Heuch et al., 1998[154]	Norway	1967–1992	< 16	Perinatal risk factors	Birth registry	Cancer registry	459	1489,297	12
Samuelsen et al., 2006 [155]	Norway	1978–1998	< 16	Head circumference at birth	Birth registry	Cancer registry	453	1 010 366	16
Kollerud et al., 2014[156]	Norway	1967–2009	< 16	Childhood exposure to radon concentrations	On-site indoor radon measurements and a buffer model with different radius size	Cancer registry	427	712 674	15
Mortensen et al., 2016 [157]	Norway	1999–2010	< 15	Folic acid intake during pregnancy	Birth registry	Cancer registry	185	687 406	11
Pershagen et al., 1992 [158]	Sweden	1982–1987	< 6	Maternal smoking	Birth registry	Cancer registry	81	148917	5
Hemminki et al., 1999 [159]	Sweden	1960–1994	< 15	Parental characteristics	Family cancer database	Cancer registry	1617	8.8milion	14
Feychting et al., 2000 [160]	Sweden	1976, 1977, 1981, and 1982	< 15	Parental occupational exposure to magnetic fields	Occupational history	Cancer registry	162	235,635	14

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Table 1 (*continued*)

Feychting et al., 2001 [24]	Sweden	1976, 1977, 1981, and 1982	< 15	Multiple exposures	Occupational history	Cancer registry	162	235,635	14
Mogren et al., 2003[161]	Sweden	1958–1994	< 15	Parental characteristics	Birth registry	Cancer registry	237	248,701	14
Rodvall et al., 2003[162]	Sweden	1965–1976	< 20	Parental occupational exposure to pesticides	Death records	Cancer registry	20	27, 329	14
Brooks et al., 2004[163]	Sweden	1983–1997	< 15	Maternal smoking during pregnancy	Birth registry	Cancer registry	480	1441,942	7
Yip et al., 2006 [20]	Sweden	1961–2000	< 15	Parental characteristics	population-based registries	Cancer registry	977	4.3 million	14
Feychting and Ahlbom, 1993[164]	Sweden	1960–1985	< 16	Parental occupational exposure to magnetic fields	Spot measurements	Cancer registry	33	558	15
Linet et al., 1996[165]	Sweden	1973–1989	< 18	Multiple risk factors	Birth registry	Cancer registry	570	2850	17
Hardell and Dreifaldt, 2001[166]	Sweden	1988–1991	< 15	Breast feeding	Medical records	Cancer registry	264	860	14
Stalberg et al., 2007[167]	Sweden	1975–1984	< 16	Prenatal exposure to diagnostic X-Ray	Birth registry	Cancer registry	512	524	15
Stalberg et al., 2008[168]	Sweden	1975–1984	< 16	Prenatal ultrasound exposure	Birth registry	Cancer registry	503	524	15
Stalberg et al., 2010[169]	Sweden	1975–1984	< 16	Prenatal medicines exposure	Birth registry	Cancer registry	512	525	15
Rossides et al., 2022[170]	Sweden	1960–2015	< 20	Parental occupational exposure to hydrocarbon solvents and engine exhaust fumes	Employment history and job exposure matrix	Cancer registry	[a]22,174	446628	19
Tettamanti et al., 2016 [171]	Sweden	1983–2010	< 15	Maternal smoking during prenatal	Birth registry	Cancer registry	1039	2577,305	15
Hauri et al., 2013[172]	Switzerland	2000–2008	< 16	Postnatal exposure to domestic radon	Estimation of in indoor radon using prediction model developed based on 35,706 measurements	Cancer registry	258	1287,354	16
Spycher et al., 2015[173]	Switzerland	1990–2000	< 16	Postnatal exposure to background ionizing radiation	Estimated external background radiation	Cancer registry	423	2093,660	16
Spycher et al., 2017[14]	Switzerland	1983–2010	< 16	Parental occupational exposure to benzene	Census records and job exposure matrix	Cancer registry	227	2803627	16
Kreis et al., 2022[174]	Switzerland	1990–2015	< 16	Postnatal exposure to NO_2	Census register	Cancer registry	668	29600	16
Coste et al., 2020[175]	Switzerland	1990–2000	< 16	Parental occupational exposure to pesticides	Census records and job exposure matrix	Cancer registry	822	3508051	15
Mazzei-Abba et al., 2021 [176]	Switzerland	1990–2016	< 16	Postnatal exposure to external background ionizing radiation	Geographic exposure models based on aerial spectrometric gamma-ray measurements	Cancer registry	701	3401,113	16
Williams et al., 2018[177]	UK, England, Wales, and Scotland	1992–2008	< 15	ART	Human Fertilization and Embryology Authority records	Cancer registry	12	12 137	8
Keegan et al., 2013[178]	UK	1962–2006	< 15	Paternal occupation and social class	Occupational data in birth registry	Cancer registry	10854	10702	14
Bhattacharya et al., 2014 [179]	UK – Aberdeen	1993–2005	< 15	Maternal and perinatal risk factors	Maternity and neonatal databank records	Cancer registry	176	704	14
Nyari et al. 2003[180]	UK- England	1975–1986	< 15	Prenatal exposure to infections	Health records	Cancer registry	161	404,106	14
Kroll et al., 2010[181]	UK- England and Wales	1962–1995	< 15	Postnatal exposure to EMF	Estimate magnetic field from high-voltage overhead power lines	Cancer registry	6584	6577	14

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Table 1 (*continued*)

Fear et al., 1998[182]	UK- England and Wales	1959–1990	< 15	Parental occupational exposure to pesticide	Death certificates	National Statistics	109	5270	14
Fear et al., 2001[183]	UK- Oxford	1956–1992	< 15	Prenatal and neonatal factors	Medical records	Hospital records	85	166	14
Cantwell et al., 2008[184]	UK-Northern Ireland	1971–1986	< 15	Perinatal risk factors	Birth records	Cancer registry	155	420 436	14
	South America								
Silva et al., 2017[185]	Brazil	2000–2010	< 15	Perinatal risk factors	Birth registry	Cancer registry	127	1564	14
	North America								
Auger et al., 2019[186]	Canada	2006–2016	4–11	Phototherapy exposure during pregnancy	Hospital records	Hospital records	264	786,998	11
Marcoux et al., 2022[187]	Canada-Quebec	2006–2019	< 15	Gestational diabetes	Medical diagnosed with gestational diabetes mellitus (glucose levels are ≥11.0 mmol/L (≥198 mg/dL))	Hospital records	360	1030,537	14
Heacock et al., 2000[188]	Canada - British Columbia	1969–1993	< 20	Parental occupational exposure to Fungicides	Parental occupational history	Cancer Registry	40	23,829	19
Spector et al., 2019[189]	USA	2004–2012	< 10	In vitro fertilization	Hospital records	Cancer registry	59	275 686	9
Francis et al., 2021[190]	USA - California	1988–2011	< 20	Parental socioeconomic status	Parental education and insurance records	Cancer registry	3022	10,791	19
Lombardi et al., 2021 [191]	USA - California	1988–2013	< 6	Postnatal exposure to Residential proximity to pesticide application	Parental education and insurance records	Cancer registry	667	123,158	5
Williams et al., 2021a[192]	USA - Minnesota	1976–2014	< 15	Perinatal risk factors	Birth certificate	Cancer registry	3166	20,589	14
Williams et al., 2021b[193]	USA - Minnesota, California, New York, Texas and Washington	1976–2014	< 15	Perinatal risk factors	Birth certificate	Cancer registry	16411	69,816	14
Contreras et al., 2016 [194]	USA - California	1988–2013	< 6	Gestational diabetes	Birth records	Cancer registry	1699	270,147	5
Heck et al., 2016[195]	USA - California	2007–2011	< 6	Parental smoking during prenatal	Birth certificates	Cancer registry	308	40,356	5
von Ehrenstein et al., 2016 [196]	USA - California	1990–2007	< 6	Ambient air exposure during prenatal and postanal periods	Geocoded addresses	Cancer registry	183	30,569	5
Wang et al., 2017[197]	USA - California	1988–2011	< 20	Parental characteristics	Birth records	Cancer registry	23,419	87,593	19
Von Behren and Reynolds, 2003[198]	USA- California	1988–1997	< 5	Perinatal risk factors	Birth records	Cancer registry	746	1491	4
MacLean et al., 2010[199]	USA- California	1988–2006	< 15	Perinatal risk factors	Birth certificates	Cancer registry	3318	14923	14
Sprehe et al., 2010[200]	USA- Texas	1995–2003	< 5	Perinatal risk factors	Birth certificate	Cancer registry	438	13331	4
Fahmideh et al., 2021 [201]	USA- Texas	1995–2011	< 17	Maternal and perinatal risk factors	Birth certificate	Cancer registry	1950	19500	16
Oksuzyan et al., 2013 [202]	USA-California	1998–2008	< 16	Perinatal risk factors	Birth registries	Cancer registry	3308	3308	15
Johnson et al., 1987[203]	USA-Texas	1964–1980	< 15	Parental occupational exposure to hydrocarbons	Birth certificates	Health registry	499	998	14
Carozza et al., 2009[204]	USA-Texas	1990–1998	< 15	Proximity to agricultural farm during postnatal	Digital orthophoto quadrangle (DOQ) data	Cancer registry	338	1802	14
Emerson et al., 1991[19]	USA-Washington	1974–1986	< 11	Perinatal risk factors	Birth certificates	Cancer registry	157	785	10
Digitale et al., 2021[205]	USA- California	1995–2017	< 12	Phototherapy exposure during postnatal period	Hospital records	Hospital records	49	139100	11
	Intercontinental								
Huang et al., 2022[206]	Denmark and China-Taiwan	1977–2016	< 20	Gestational Diabetes	Hospital and health insurance records	Cancer registry	44	1307	14

[a] Total cases in some publications were summed-up with other types of childhood cancer but the actual numbers for CBT were not made available despite separating the risk estimates for CBT

The majority of articles ($n = 68$; 38%) were published between 2010 and 2019, followed by those published before the year 2000 (i.e. 1976–1999, $n = 51$; 28%). Forty-one studies, representing 23%, were published from 2000 to 2009, while the remaining ($n = 21$; 11%) were recently published. Cases included in the eligible studies were diagnosed between 1953 and 2017 (Table 1).

3.3. Quality assessment and bias

Out of 181 articles critically appraised for quality using the JBI tools, case-control studies had a slightly higher average score (87.9%) compared to cohort studies (80.2%). We did not exclude articles based on quality, as none was "critically low". Hence, all screened articles appraised were included in the final analysis. The assessment grading for the different components of each study is shown in appendix pp 14–19.

Birth and parental characteristics (Fig. 2 and appendix pp 20–37, 72–73).

Children conceived through *assisted reproductive technology (ART)* showed no association with CBT in 2 case-controls studies [53,64] but was positively associated when 4 cohort studies [121,145,177,189] were pooled and in the combined analysis. Heterogeneity across case-control studies was "probably unimportant", "no heterogeneity" was recorded for cohort studies and in combined analysis.

Gestational age of children < 37 weeks at birth was not associated with CBT in neither case-control nor cohort studies based on 5 [18,30,53,63,111] and 15 studies [17,19,125,127,131,154,165,179,183,184,193,198–201], respectively. This measure was strongly affected by considerable heterogeneity across the cohort studies, with p value < 0.01. There was no association with gestational age > 40 weeks based on 5 case-control studies [18,30,53,64,111], but there was a borderline association when 12 cohort studies were pooled [17,125,154,161,165,184,193,198–202].

'*Small for gestational age*' (SGA) did not show increased risk for CBT based on 3 [53,66,71] case-control and 5 cohort studies [16,17,199,200,202]. Regarding 'large for gestational age' (LGA) no increased risk was observed based on 3 case-control studies [53,66,71] but we observed some support of an association with CBT when 6 cohort studies were pooled [16,17,123,199,200,202], the association was somewhat attenuated in the combined analysis. Little evidence for an association was observed for the subtypes of CBT.

Caesarean delivery was not associated with CBT in case control studies (4 studies) [63,67,71,81]. Conversely, we observed some positive associations in cohort studies of CBT (9 studies) [120,129,131,143,165,179,183,198,201] and of certain subtypes (astrocytoma 3 studies and embryonal 2 studies). The associations remained only among CBT in combined analysis. Heterogeneity was moderate across studies. We were not able to distinct between elective or emergency Caesarean section in the meta-analysis due to lack of data provided by the original studies.

Birth order (5 case-control studies [53,64,71,76,111]; 4 cohort studies [17,154,199,207]) did not show increased association with CBT. Similarly, *breast feeding* (<6 months [30,64,68,82,108,208,209] and ≥6 months [30,59,64,82,209]), *day care attendance* [60,76] and "*parity*" [70,120,161] (2 or 3 and ≥3) showed null association with CBT. Most studies used birth order and parity 1 as reference group.

Birthweight < 2500 g were associated with CBT, based on 9 case-control studies [18,30,53,63,64,66,68,77,111]. The association was weaker based on 15 cohort studies [16,17,120,127,161,165,179,183–185,198–202], and stronger for embryonal tumours but was somewhat attenuated in the combined analysis. However, this was impacted by "considerable" heterogeneity across the cohort studies and in combined analysis, with p value < 0.01 for both heterogeneity and small-study effects, respectively. *Birthweight* > 4000 g was associated with CBT after pooling 9 case-control studies [18,30,53,63,64,66,68,77,111]. This was also seen in embryonal and "other glioma" subtypes of the cohort studies but not for total CBT in 14 cohort studies [16,17,19,120,127,154,161,184,185,198–202] and in combined analysis. Again, we observed considerable heterogeneity (p value <0.01) across cohort studies and in combined analysis.

Head circumference > 38 cm at birth showed a 2-fold association with CBT based on 3 cohort studies [16,17,155] and the 2-fold association remained in combined analysis (all 3 studies were from the Nordic countries). Those with head circumference < 33 cm did not show increased risk with CBT based on the same 3 studies [16,17,155]. Heterogeneity was considerable and substantial in both circumstances, respectively.

Mothers' age at birth (<25 and ≥35 years old) was not associated with CBT in case-control (4 studies) [37,64,81,118] and cohort studies (9 studies) [21,120,125,154,161,165,184,197,198], separately or when combined. Likewise, *fathers' age at birth* (≥35 years for case-control studies [34,64,200]; <25 [21,154,184,198] and ≥35 years [21,125,154,184,198] for cohort studies) was not associated with CBT.

Ionising and non-ionising radiation (Fig. 3 and appendix pp 38–49).

Maternal exposure to x-rays (8) [30,34,46,56,61,68,84,183] during pregnancy did not show an association with CBT in case-control studies. Also, children exposed to x-rays during childhood were not associated with CBT in 7 case-control studies [34,42,56,61,85,97,131] and in the combined analysis. Children exposed to CT scans did not show an association (3 case-control studies [56,61,210]), but were associated with CBT in cohort studies (6) [119,126,128,149,151,152] and in combined analysis. Children exposed to domestic radon [156,172] and external background ionizing radiation during childhood were observed to have some support of an associations based on each 2 cohort studies [176,211].

Maternal exposure to ultrasound (4 studies) [42,46,61,78] and electric heated waterbed (4 studies) [58,91,105,117] during pregnancy did not show association with CBT in case-control studies. In contrast,

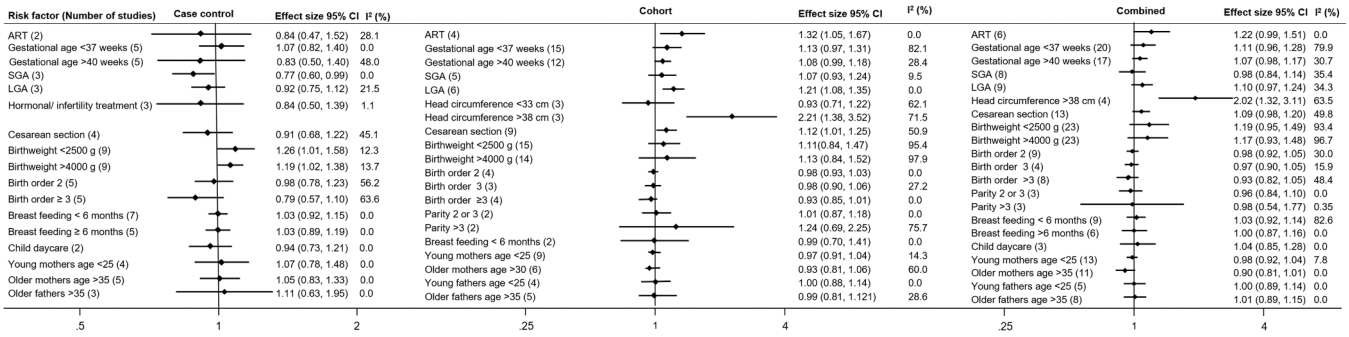

Fig. 2. Meta-analysis of pooled effect sizes (ES) of exposure to birth and parental characteristics for the risk of CBT and heterogeneity, by study design.

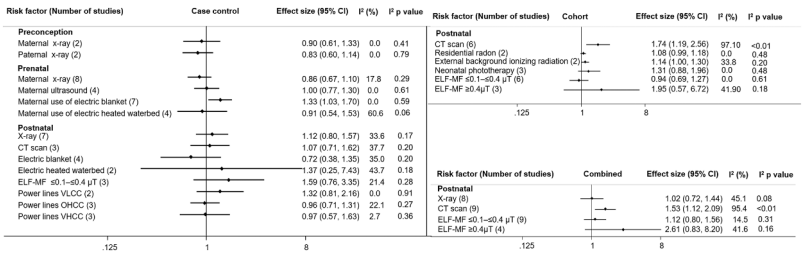

Fig. 3. Meta-analysis of pooled effect sizes (ES) of exposure to ionising and non-ionising radiation for the risk of CBT and heterogeneity, by study design.

we observed an association for maternal use of electric blankets during pregnancy and CBT based on 7 case-control studies [30,58,91,97,105,109,117]. History of neonatal phototherapy, a treatment of postnatal jaundice with visible blue light, was not associated with CBT based on 3 cohort studies [183,205,212], with moderate heterogeneity between studies.

Children exposure to ELF-MF $\leq$ 0.1–$\leq$ 0.4 μT (3 case-control [44,79,113] and 6 cohort studies [130,132,148,153,160,181]) or to ELF-MF $\geq$ 0.4μT (3 cohort studies [130,148,181]) during childhood were not associated with CBT, not separately and not in combined analysis. Exposure to powerlines (Very Low Current Configuration (VLCC), Ordinary High Current Configuration (OHCC), and Very High Current Configuration (VHCC)) based on 3 case-control studies was not associated with CBT [111,117,213]. Childhood exposure to electric blankets [47,58,117,213] and electric heated waterbeds [58,117] did not show associations with CBT based on 4 and 2 case-control studies, respectively.

3.4. Parental and childhood exposures to pesticides and other chemicals

(Table 2 and appendix pp 50–68, 74–75).

Children's exposure to domestic herbicides [96,106] and insecticides [22,30,96,106] were associated with CBT in case-control studies (2 and 4, respectively). It was however weak in childhood exposure to general domestic pesticides based on 6 case-control studies [22,30,34,49,96,112]. No association was observed in children who lived on a farm and those who were in contact with livestock based on each 3 case-control studies [34,62,102].

Children whose mothers were exposed to domestic insecticides during pregnancy were associated with CBT (4 case-control studies) [49,96,106,112] but not for herbicides [96,106] (2 case-controls studies), and when maternal prenatal general domestic pesticide exposure was considered [34,49,96,112] (4 case-controls studies), an association was observed in the combined analysis. Maternal occupational exposure to general pesticides [88,97,99] during preconception/prenatal period [88,97,99] did not show any association with CBT or any individual CBT types but of astrocytoma for fungicides exposure based on 2 case-control studies. Children whose parents were farmers/ resident in farmlands before conception (fathers) [35,103,115,178] and during pregnancy (mothers) [34,62,71,87,102] were not associated with CBT based on case-control studies (4 and 5 studies, respectively) and in combined analysis.

Children whose fathers were occupationally exposed to general pesticides during preconception or prenatally were associated with CBT based on 3 case-control studies [23,88,99] and in the combined analysis, but not in the 4 cohort studies [24,175,182,188] separately. The association was stronger among astrocytoma for fungicides and herbicides based on 2 case-control studies. Paternal exposure to livestock before conception showed an association with CBT based on 2 cohort studies [135,178].

Paternal exposure to benzene before conception was associated with CBT when 4 case-control studies were pooled [57,93,103,116], but not in the 3 cohort studies [14,24,214]. The combined analysis showed a 1.5-fold association (95% CI 1.09–2.41), with low heterogeneity. A similar association was observed for astrocytoma based on 2 case-control studies with no heterogeneity. Maternal benzene exposure before conception was associated with a 2-fold odds of CBT based on 2 case-control studies [57,103]. Benzene exposure during childhood was neither associated with astrocytoma nor with embryonal tumours [133,196]. It was also the same for childhood exposure to NO_2 based on 2 cohort studies [142,174]. Exposure to diesel engine exhaust before conception/during pregnancy (mother) was not associated with CBT based on 2 case-control studies [52,83] but was associated in combined analysis, and in 3 cohort studies for paternal exposure before conception [137,146,178]. Parental exposure to general solvents before conception or during pregnancy did not show an association with CBT in 2 case-control (mothers) [57,83] and 2 cohort studies [24,178] (fathers), nor in the combined analysis.

Paternal exposure to paper [116,203] and textile [24,138,178] dusts before conception was not associated with CBT based on 2 case-control and 3 cohort studies, respectively. Paternal wood dust exposure was associated with CBT based on 3 case-control studies, with no heterogeneity across the studies [24,138,178].

Paternal occupational exposure as a painter around preconception was slightly elevated based on 2 case-control studies [55,203], and was associated with CBT in 4 cohort studies [24,136,146,178], as well as in the combined analysis. No association for maternal occupational exposure as a painter during pregnancy was observed in case-control studies [55,215], with no heterogeneity across studies.

Lifestyle and medical history (Table 3 and appendix pp 69–70, 76).

Maternal coffee consumption $\geq$ 2 cups/day during pregnancy was associated with CBT, based on 3 case-control studies [34,54,65], but maternal tea [54,65] and alcohol consumption [30,50,65,71,84,97] during pregnancy were not associated with CBT when 2 and 6 case-control studies were assessed, respectively. However, there was substantial heterogeneity for maternal alcohol consumption.

Maternal smoking > 10 cigarettes per day during pregnancy was associated with CBT, based on 4 cohort studies [158,163,165,171]. However, smoking without quantification and before conception showed no association based on 17 case-control studies [34,36,37,46,51,63,65,72,74,84,86,92,101,104,106,122,216] and in combined analysis. Paternal smoking around conception [51,65,74,104] and during pregnancy [36,43,51,72,84,86,92,101], only available in case-control studies, were associated with CBT.

Maternal intake of vitamin and folic acid during pregnancy was inversely associated with CBT in 2 cohort studies [157,169], but did not show an association in 7 case-control studies [34,37,48,63,73,90,100].

Maternal intake of cured meat during pregnancy was associated with CBT, based on 5 case-control studies [34,46,94,100,106].

Maternal obesity during pregnancy was not associated with CBT in 2 cohort studies [21,124] nor in combined analysis, but gestational diabetes during pregnancy was elevated based on 4 cohort studies and in the combined analysis [147,187,194,206] (Appendix pp 71).

Sensitivity analyses

In sensitivity analysis, there was no substantial heterogeneity in studies across the decades of study publication. However, we noted that the increased risk of CBT in relation to paternal exposure to benzene was only observed in the earliest studies (before the year 2000), while for

Table 2
Meta-analysis of pooled effect sizes (ES) of exposure to pesticides and other chemicals for the risk of CBT and heterogeneity (I^2) between studies, by study design.

		Case-control							Cohort							Combined						
Risk factor	Window period	N	ES	LCI	UCI	I^2 (%)	I^2 p value	Egger's p value	N	ES	LCI	UCI	I^2 (%)	I^2 p value	Egger's p value	N	ES	LCI	UCI	I^2 (%)	I^2 p value	Egger's p value
Child domestic pesticides and benzene exposure																						
General pesticides	Postnatal	6	1.13	0.88	1.45	0	0.18	0.09														
Insecticides	Postnatal	4	1.44	1.20	1.73	0	0.65	0.13														
Herbicides	Postnatal	2	2.38	1.31	4.33	0	0.50	-														
Farm residence	Postnatal	3	1.39	0.51	3.81	77.2	0.01	0.71														
Contact with livestock	Postnatal	3	1.05	0.54	2.04	76.6	0.01	0.04														
Child's benzene	Postnatal	2	1.00	0.93	1.07	0	0.52	-														
Maternal domestic pesticides																						
General pesticides	Prenatal	4	1.16	0.80	1.68	43	0.13	0.15								5	1.25	1.04	1.50	20.1	0.27	0.37
Insecticides	Prenatal	4	1.45	1.09	1.94	0	0.86	0.99														
Herbicides	Prenatal	2	1.07	0.51	2.27	0	0.86	-														
Farm residence	Prenatal	5	1.83	0.67	5.05	82.6	< 0.01	0.20								6	1.64	0.73	3.70	79.0	< 0.01	0.12
Farm residence	Preconception	4	0.97	0.60	1.59	0	0.88	0.051														
Maternal occupational pesticides																						
Pesticides	Preconception/ prenatal	3	1.15	0.92	1.42	14.8	0.30	0.08														
Paternal occupational pesticides																						
Paternal general pesticides	Preconception/ prenatal	3	1.48	1.23	1.77	0	0.64	0.27	4	1.12	0.70	1.80	73.6	0.01	0.25	7	1.34	1.06	1.70	63.0	< 0.01	< 0.01
Contact with livestock	Preconception								2	1.33	1.06	1.68	0	0.68	-							
Farm residence	Preconception	4	1.08	0.78	1.51	42.4	0.16	0.04								5	1.27	0.87	1.87	61.2	0.03	0.01
Occupational exposure to other chemicals																						
Maternal occupational paint	Prenatal	2	0.92	0.70	1.20	0	0.87	-														
Maternal solvent	Preconception/ prenatal	2	1.19	0.83	1.71	0	0.87	-								3	1.14	0.85	1.53	0.0	0.91	0.15
Maternal benzene	Preconception	2	2.22	1.01	4.88	0	0.96	-														
Maternal benzene	Prenatal								2	0.94	0.75	1.18	0	0.74	-	3	0.94	0.75	1.16	0.0	0.74	0.25
Paternal occupational paint	Preconception	2	1.29	0.90	1.85	0	0.67	-	4	1.56	1.02	2.40	56.4	0.08	0.44	6	1.41	1.10	1.81	30.1	0.21	0.65
Paternal solvent	Preconception/ prenatal								2	1.06	0.90	1.25	0	0.73	-	3	1.10	0.95	1.27	0.0	0.61	0.36
Paternal benzene	Preconception	4	1.74	1.10	2.76	0	0.54	0.80	3	1.37	0.78	2.41	32.6	0.23	0.18	7	1.50	1.09	2.07	0.0	0.43	0.19
Diesel engine exhaust and organic dust																						
Maternal diesel engine exhaust	Preconception	2	1.41	0.56	3.54	0	0.88	-								3	1.33	1.01	1.74	0.0	0.97	0.43
Paternal diesel engine exhaust	Preconception/ prenatal								3	1.02	0.94	1.11	0	0.37	0.26	4	1.03	0.95	1.11	0.0	0.56	0.43
Paternal exposure to paper dust	Preconception	2	1.91	0.82	4.44	0	053	-								3	1.37	0.81	2.31	0.0	0.74	0.05
Paternal exposure to textile dust	Preconception								3	0.95	0.75	1.19	0	0.77	0.80							
Paternal exposure to wood dust	Preconception								3	1.15	1.00	1.32	0	0.59	0.41							

N = Number of studies; ES= Effect size; LCI=Lower confidence interval; UCI=Upper confidence interval; I^2 = Heterogeneity

Table 3
Meta-analysis of pooled effect sizes and heterogeneity evaluating association between lifestyle and the risk of CBT.

		Case-control						Cohort						Combined					
Risk factor	Window period	N	ES	LCI	UCI	I^2 (%)	I^2 p value	N	ES	LCI	UCI	I^2 (%)	I^2 p value	N	ES	LCI	UCI	I^2 (%)	I^2 p value
Maternal exposures																			
Maternal tea	Prenatal	2	1.14	0.88	1.47	26.70	0.24												
Maternal tea $\geq$ 2 cups/day	Prenatal	3	1.09	0.79	1.49	27.20	0.25												
Maternal coffee	Prenatal	2	1.11	0.90	1.35	1.7	0.31												
Maternal coffee $\geq$ 2 cups/day	Prenatal	3	1.45	1.07	1.95	0	0.72												
Maternal alcohol	Prenatal	6	1.19	0.83	1.70	78.5	< 0.01												
Maternal smoking	Prenatal	17	1.08	0.93	1.25	48.5	0.01	5	1.03	0.82	1.29	31.9	0.21	22	1.06	0.94	1.20	43.4	0.02
Maternal smoking	Preconception	5	1.04	0.85	1.28	14.4	0.32												
Maternal smoking 1–10 cig/day	Prenatal	7	0.97	0.71	1.32	63.7	0.01	3	1.11	0.93	1.31	0	0.67	10	1.01	0.82	1.25	54.3	0.02
Maternal smoking $>$ 10 cig/day	Prenatal	8	1.06	0.83	1.35	21.3	0.26	4	1.18	1.00	1.40	0	0.88	12	1.11	0.97	1.26	0.0	0.45
Maternal vitamin and folic acid	Prenatal	7	0.72	0.44	1.19	74.8	< 0.01	2	0.65	0.44	0.96	0	0.76	9	0.72	0.49	1.05	68.8	< 0.01
Maternal Vitamin, folate and/or iron	Prenatal	2	0.69	0.27	1.80	85.7	0.01												
Cured meat	Prenatal	5	1.51	1.05	2.17	28.6	0.21												
Maternal obesity	Prenatal							2	1.14	0.44	2.99	75.4	0.02	3	1.01	0.57	1.78	63.8	0.041
Gestational diabetes	Prenatal							4	1.19	0.98	1.44	0	0.85	5	1.17	0.96	1.41	0.0	0.84
Paternal exposures																			
Paternal smoking	Prenatal	8	1.15	1.00	1.32	0	0.99												
Paternal smoking	Preconception	4	1.15	1.00	1.32	0	0.80												
Paternal smoking $>$ 10 cig /day	Prenatal	3	1.01	0.86	1.18	0	0.91												
Paternal smoking $<$ 15 cig /day	Prenatal	4	1.08	0.92	1.28	0	0.63												
Paternal smoking $>$ 15 cig /day	Prenatal	3	0.98	0.83	1.17	0	0.66												
Paternal smoking 1–20 cig /day	Prenatal	4	1.08	0.94	1.24	0	0.78												
Paternal smoking $>$ 10 cig /day	Preconception	4	1.06	0.93	1.21	0	0.44												
Paternal smoking $>$ 20 cig /day	Preconception	2	1.02	0.85	1.23	0	0.89												
Paternal smoking 1–20 cig /day	Preconception	4	1.16	0.99	1.36	0	0.63												

N = Number of studies; ES= Effect size; LCI=Lower confidence interval; UCI=Upper confidence interval; I^2 = Heterogeneity

children delivered via Caesarean section we found increased risks in the most recent studies (2020–2022) compared to those published in before then (Appendix pp 77).

There was heterogeneity across the continents for gestational age < 37 weeks, which was associated with CBT only in Australia and not in Europe and North America (p value = <0.01). The heterogeneity was also seen for maternal age ≥ 35 years and maternal smoking during pregnancy, where we observed an increased risk of CBT only for studies published in Asia and Europe. Without heterogeneity, birthweight ≥ 4000 g was associated with CBT among studies published in Europe and America but not in Australia. Childhood exposure to CT scans was observed to be associated with CBT among studies published in Asia but was attenuated in Australia and Europe (Appendix pp 77).

4. Discussion

To our knowledge, this is the largest comprehensive systematic review and meta-analysis, assessing over 60 potential risk factors for CBT with data from 181 articles with cases diagnosed between 1953 and 2017. The most consistent findings were for birthweight (<2500 g and >4000 g), where the association was observed both in case-control and cohort studies separately, and when combined. Maternal domestic exposure to insecticides during pregnancy, consumption of cured meat and ≥ 2 cups/day of coffee during pregnancy, and paternal occupational exposure to general pesticides and benzene were associated with CBT in mainly case-controls studies. Furthermore, ART, Caesarean section, gestational age > 40 weeks, LGA, head circumference > 38 cm, childhood exposure to CT scans, paternal occupational exposure to paint before conception and maternal smoking of > 10 cigarettes per day during pregnancy were associated with CBT in cohort studies, but lesser so in case-control studies. Maternal use of electric blanket during pregnancy and paternal occupational exposure to wood dust were associated with CBT and were reported only by case-control studies. SGA and maternal intake of vitamins and folic acid during pregnancy were inversely associated with CBT in case-control and cohort studies, respectively. However, gestational age < 37 weeks, birth order (2 and ≥3), hormonal/ infertility treatment, parity (2 and ≥3), breastfeeding (< 6 months and ≥6 months), child day-care attendance, parental age, childhood and parental exposure to X-ray, maternal exposure to ultrasound, heated waterbed, tea and alcohol drinking during pregnancy were not associated with CBT neither in case-control nor in cohort studies.

Regarding strengths of associations, 216 potential risk factors including main and sub-categories of exposures had a strength less than 1.5 (with 2 inversely associated), 12 others were between 1.5 and 2.0, and 3 potential risk factors including domestic herbicides, head circumference > 38 cm at birth and maternal exposure to benzene before conception had ES with magnitude > 2.0 (Fig. 4).

Included articles were of high or moderate quality as per the quality analysis outcome. While half of the articles came from Europe, none was reported from Africa, despite the continent having over 670 million children under the age of 18 [217]. Most African nations lack effective regulatory enforcement against exposures to known carcinogens [218]. This necessitates immediate attention, for researchers, funders, and policy makers to address this research gap by developing study hypotheses and regulations that will result in the prevention and control of paediatric cancer [219].

For most associations, we observed inconsistent and to some extent contradicting results in cohort/ registry studies and interview-based case-control studies, which complicates the interpretation and raises questions of the validity of our summary results as well as previous assessments. Cohort studies are large, and exposures are derived from standardized census data and/or hospital records but often include few cases. Registry-based case-control studies are large in numbers and the exposure data comes from different sources including censuses, hospital records, and other register data collected in a standard manner. Nested case-control studies are considered free from selection bias and also from recall bias, if exposure information was collected before the CBT was diagnosed. However, if the study participants were contacted after diagnosis to collect more precise information, they may encounter the same issues as traditional case-control studies including differential recall and selection bias from dropouts. Traditional case-control studies which require contact with the study participants are often limited in size and the control population can suffer from low participation or a biased sampling frame. While information such as on domestic use of pesticides and amount of smoking is more detailed, and more precise regarding the time of exposure, it may suffer from limited reporting accuracy years after the event or exposure and the recall can differ

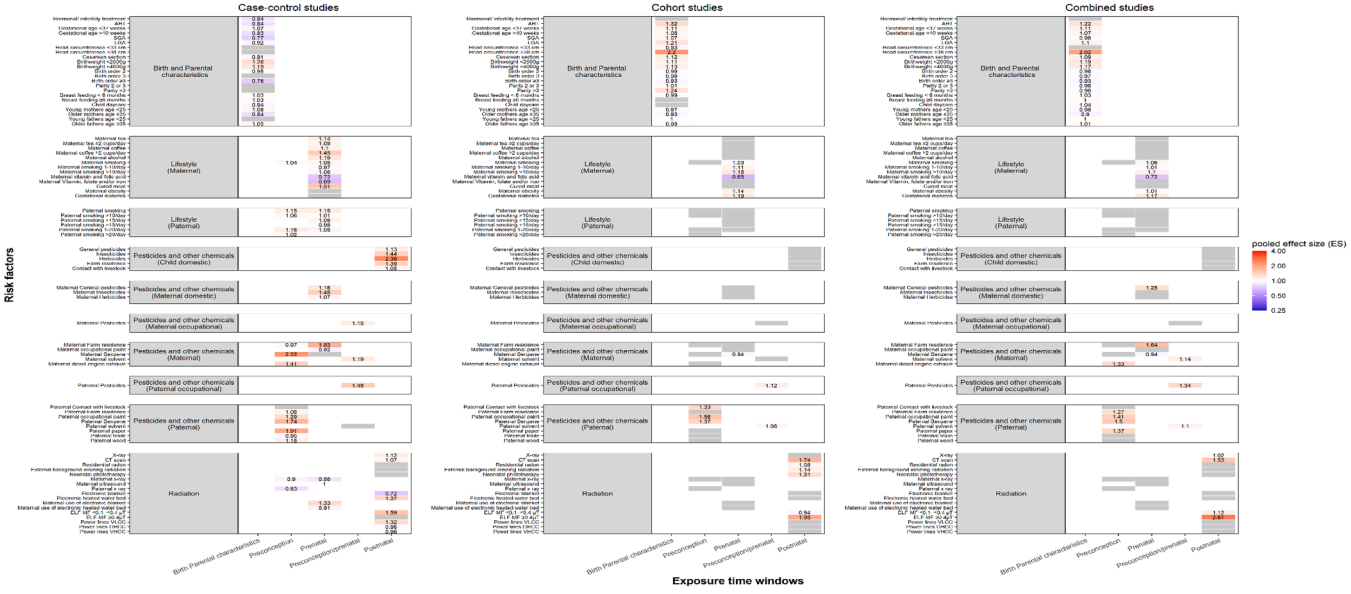

Fig. 4. Heatmap of effect sizes obtained from meta-analyses evaluating associations between exposures and the risk CBT by study design (case and cohort studies, and combined analysis), exposure medium/time window. Pooled effect sizes obtain from meta-analyses evaluating associations between exposures and the risk of CBT by study type, exposure medium/time window. The more intense the red colour, the larger the ES value. ES estimates greater than 1 are denoted in shade of red, while ES < 1 are in blue. Numbers denote ES estimates. Cells with grey colour denote either the absence of results or a risk factor-exposure medium/time window.

between cases and controls, leading to bias away from the null effect.

The observed associations with high birthweight (>4000 g), head circumference > 38 cm, gestational age > 40 weeks and LGA, confirms the findings of previous reviews [26,27]. They support the hypothesis that CBT could originate *in utero* [17]. These intrinsic factors are potentially interrelated and linked to intrauterine cell proliferation and thus could increase susceptibility to malignant transformation, induced by growth hormone (GH) variant gene on chromosome 17 responsible for regulation of maternal insulin-like growth factor-1 (IGF 1) [17,220, 221]. Moreover, overexpression of IGF component and disorder in chromosome 17 have been implicated in brain tumour development [17, 222,223] Although, our findings were dominated by results from cohort studies, recall and selection biases may have affected the case-control studies. In sensitivity analysis, high birthweight was associated only in recent decades and in Europe and North America, with the stronger association in the latter. This outcome may imply that there is an underlying factor driving this association in recent years, especially in the two continents.

Overall, children conceived through ART and those delivered through CS showed weak association with CBT. The stronger association observed for CS in most recent years maybe be due to increased prevalence, especially in North America where 1 out of 3 births are delivered through CS [224].

For the increased risk we observed in combined analysis of case-control and cohort studies for children exposed to CT scans, the results were driven by higher magnitude of association in cohort studies (1.35–2.56) except for Foucault et al. [149] (1.06) in France. The magnitudes were lower in case-control studies. Response and recall biases may have played a role in this outcome, especially as one of the studies (Milne et al. [56]) used mailed questionnaires to obtain medical and exposure data [56,225]. This finding is similar to a previous systematic review conducted by Huang et al. [226] who observed elevated risk estimates but with wide CIs. In sensitivity analysis of our review, a stronger association was observed in Asia, attenuated in Australia, and further attenuated in Europe. A recently published large-scale cohort study of almost 1 million children and adolescents who had CT scans with their organ doses estimated from data received from radiology departments, showed an increased risk of brain tumours but participants were followed into adulthood [227].

Children with history of neonatal phototherapy was only elevated in our review with a low magnitude of association (1.3), it was only investigated in three cohort studies. This finding is in line with a review by Wang et al. who stated that UV light exposure causes gene mutations thus increasing the risk of cancer [228]. Electric blankets are known sources of EMFs for *in utero* exposure during pregnancy. Its association with CBT has been reported in single case-control studies only but not in reviews, except the present in the study. However, as electric blankets were the only source of EMF showing positive results while for other major EMF sources this was not confirmed (like EMF from power lines), recall bias may have played a role. Childhood and parental exposure to X-rays, ultrasound and heated waterbed during pregnancy were not associated with CBT.

The stronger associations reported for children exposed to herbicides and insecticides at home, and for mothers (insecticides) were mostly from case-control studies. Our findings are similar to previous reviews linking parental exposure to pesticides before or during foetal intrauterine life and childhood to CBT [26,229–231]. North American children whose fathers were occupationally exposed to pesticides had higher risk estimates of CBT compared to the European children, in sensitivity analysis. This outcome is in line with the report of the Food and Agriculture Organisation of the United Nation (FAO), who stated that Americas applied the highest level of pesticides globally, with the USA being the largest user of pesticides in 2020 [232].

The overall association we found for paternal exposure to benzene before conception was driven by the case-control studies. Alongside maternal exposure to benzene which was only investigated in case-control studies. This may be attributed to detailed exposure assessment information obtained from the participants. However, potential exposure misclassification may have attenuated or strengthened the outcome. The association was stronger in North America prior to the year 2000 but lower in other decades. This outcome in the sensitivity analysis may be explained by better benzene regulation in recent years. The studies assessed parental occupational exposure to benzene using job history via self-reporting questionnaire instruments or telephone interviews and coded to a locally developed [116] or international occupational classification [57]. For maternal exposure to diesel engine exhaust and paternal exposure to wood dust, exposures were also assessed with similar methods. Our findings agree with those of Johnson et al. [26] on diesel engine exhaust but no other review has reported wood dust exposure and CBT. For self-report occupational exposures in childhood cancer case-control studies methodological investigations have shown that there is indeed concern about recall bias potentially inflating the observed associations [225].

The association we observed for maternal coffee consumption of ≥ 2 cups/day during pregnancy has previously only been reported in relation to childhood leukemia, but not for CBT [233–235]. The observed association for paternal smoking we noted, agreed with previous reviews [26,28]. In sensitivity analysis, estimates were higher in Asia, some support of association for Europe but not so for Australia and North America. Consumption of cured meat including hot dogs, bacon, sausages, ham etc during pregnancy was associated with CBT, these findings are confirmed by previous reviews [26,29]. Mothers of children with brain tumours have reported more frequent eating of cured meats during pregnancy compared with mothers of controls [91] It is suggested that N-nitroso compounds (NOCs) and NOC precursors in cured meat may play a role in initiation of brain tumours during human foetal development. Since NOCs are potent neuro-carcinogens in non-human primates and other animals, especially when exposure occurs *in utero* [236–240].

Our review was limited by the large proportion of case-control studies (47%), as direct contact with each study participant includes concern of selective participation and differential recall. On the other hand, it allows collection of information that is not available in registry-based studies and more detailed information and more precise timing of the exposure. Most studies are underpowered for analyses by histological types of CBT; the International Classification of Childhood Cancers [11] has also changed over time so it is challenging to compare sub-type specific results across studies that were conducted in different decades. Also, aggregating one histological type over others may have diluted or fortified some associations. The number of cases for some risk factors in single studies were not reported by the authors of those articles. Our study includes a well-structured search strategy which allowed us to retrieve a large volume of eligible articles making it possible to conduct meta-analysis by study design (case-control and cohort studies), group of persons exposed (paternal, maternal and childhood), exposure time window (preconception, prenatal and postnatal) and to some extent types of CBT (astrocytoma, embryonal, ependymomas and “other gliomas”). Furthermore, we conducted stratified analyses by publication decades and by continents. The extracted risk estimates included in the meta-analysis were mainly adjusted models (e.g. at least age and sex).

Birth characteristics do not necessarily mean that they are the underlying risk factors; they can also be proxies of prenatal events or conditions that potentially are associated with CBT. Therefore, birth characteristics associated with CBT should be interpreted with special caution, as they can represent intermediate factors rather than being risk factors for CBT.

5. Conclusion

This comprehensive review and meta-analysis showed several associations between modifiable risk factors and CBT. This included ART, Caesarean section, childhood and maternal domestic exposure to

pesticides, parental occupational exposure to pesticides and benzene, paternal occupational exposure to paint and wood dust, maternal exposure to diesel engine exhaust before conception, paternal and maternal smoking, maternal drinking of coffee ≥2 cups/day during pregnancy, and consumption of cured meat. Inverse associations were seen for maternal intake of vitamin and folic acid. However, our results should be interpreted with caution, especially as results for most risk factors were discordant by study design and a causal interpretation for most is not established. Finally, improved exposure assessment is needed in further studies to obtain solid evidence of modifiable risk factors of CBT.

Disclaimer

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2023.102510.

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