Article:
Schraw, Jeremy M, Petridou, Eleni Th, Bonaventure, Audrey et al. (13 more authors) (2023) Breastfeeding and risk of childhood brain tumors : a report from the Childhood Cancer and Leukemia International Consortium. Cancer causes and control. pp. 1005-1015. ISSN 1573-7225

https://doi.org/10.1007/s10552-023-01746-3

Breastfeeding and Risk of Childhood Brain Tumors: A Report from the Childhood Cancer and Leukemia International Consortium

Jeremy M. Schraw[1,2], Eleni Th. Petridou[3,4], Audrey Bonaventure[5], John D. Dockerty[6], Maria Karalexi[4], Evangelia Ntzani[7,8], Claire Infante-Rivard[9], Jacqueline Clavel[5,10], Paige M. Bracci[11,12], Roberta McKean-Cowdin[13], Eve Roman[14], Eleanor Kane[14], Friederike Erdmann[15,16], Joachim Schüz[17], Beth A. Mueller[18,19], Michael E. Scheurer[1,2]

1. Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX USA.
2. Center for Epidemiology and Population Health, Department of Pediatrics, Baylor College of Medicine, Houston, TX USA.
3. Department of Hygiene, Epidemiology, and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece.
4. Hellenic Society for Social Pediatrics and Health Promotion, Athens, Greece.
5. CRESS, Université de Paris, INSERM UMR-1153, Epidemiology of childhood and adolescent cancers team, Villejuif, France.
6. Department of Preventative and Social Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand.
7. Center for Evidence-Based Medicine, Department of Health Services, Policy and Practice, School of Public Health, Brown University, Providence, RI USA.
8. Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, 45110 Ioannina, Greece.
9. Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montréal, Québec, Canada.
10. National Registry of Childhood Cancers, APHP, Hôpital Paul-Brousse, Villejuif, and CHU de Nancy, Vandoeuvre-lès-Nancy, France.
11. Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA USA.
12. Hellen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA USA.

13. Keck School of Medicine, University of Southern California, Los Angeles, CA USA.
14. Epidemiology and Cancer Statistics Group, Department of Health Sciences, University of York, York, United Kingdom.
15. Environment and Lifestyle Epidemiology Branch, International Agency for Research on Cancer, World Health Organization (IARC/WHO), Lyon, France.
16. Division of Childhood Cancer Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center Mainz, Mainz, Germany.
17. Section of Environment and Radiation, International Agency for Research on Cancer (IARC/WHO), Lyon, France.
18. Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA USA.
19. Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA USA.

Corresponding author:

Jeremy M. Schraw, PhD

Assistant Professor

Section of Hematology/Oncology, Department of Pediatrics

Baylor College of Medicine

Houston, TX USA

Phone: +1 (713-798-2924) | Email: schraw@bcm.edu | ORCID: 0000-0002-6674-9562

ACKNOWLEDGMENTS

The representatives of the NARECHEM-ST Study wish to thank Evdoxia Boukai, MPH, and George Markozannes, MSc, for their contributions to the work.

The representatives of the Texas Study wish to thank Tiffany Chambers, MPH, Elwin Jaime, MS, and Sofia M. Olivares De La Mora for their assistance with data management and data analysis.

ABSTRACT

PURPOSE: Studies report mixed findings regarding the association of breastfeeding with childhood brain tumors (CBT), the leading causes of cancer-related mortality in young people. Our objective was to determine whether breastfeeding is associated with CBT incidence. **METHODS:** We pooled data on N=2,610 cases with CBT (including 697 cases with astrocytoma, 447 cases with medulloblastoma/primitive neuroectodermal tumor [PNET], 167 cases with ependymoma) and N=8,128 age- and sex-matched controls in the Childhood Cancer and Leukemia International Consortium. We computed unconditional logistic regression models to estimate the odds ratio (OR) and 95% confidence interval (CI) of CBT, astrocytoma, medulloblastoma/PNET, and ependymoma according to breastfeeding status, adjusting for study, sex, mode of delivery, birthweight, age at diagnosis/interview, maternal age at delivery, maternal educational attainment, and maternal race/ethnicity. We evaluated any breastfeeding versus none and breastfeeding ≥6 months versus none. We subsequently performed random effects meta-analysis to confirm our findings, identify potential sources of heterogeneity, and evaluate for outliers or influential studies. **RESULTS:** Breastfeeding was reported by 64.8% of control mothers and 64.5% of case mothers and was not associated with CBT (OR 1.04, 95% CI 0.94-1.15), astrocytoma (OR 1.01, 95% CI 0.87-1.17), medulloblastoma/PNET (OR 1.11, 95% CI 0.93-1.32), or ependymoma (OR 1.06, 95% CI 0.81-1.40). Results were similar when we restricted to breastfeeding ≥6 months and in meta-analyses. **CONCLUSION:** Our data suggest that breastfeeding does not protect against CBT.

KEYWORDS

childhood brain tumors; childhood cancer; epidemiology; breastfeeding; infant feeding; Childhood Cancer & Leukemia International Consortium.

INTRODUCTION

Brain tumors have overtaken leukemia as the leading cause of cancer-related death in children and adolescents [1, 2]. Childhood brain tumors (CBTs) encompass many histologically distinct subtypes, the most common being glioma, medulloblastoma, and primitive neuroectodermal tumors (PNET) [3, 4]. Ionizing radiation is an established risk factor, as are Cowden, Gorlin, Li-Fraumeni, Rubinstein-Taybi, Turcot, and Von Hippel-Lindau syndromes, tuberous sclerosis, and neurofibromatosis types 1 and 2 [2, 4]. However, the proportion of CBTs attributable to *de novo* or inherited genetic variants is believed to be small [5, 6], suggesting a role for environmental factors in their etiology.

Both parent and child factors may be associated with CBTs. Suspected parental risk factors include older age [7, 8] and exposure to pesticides or polycyclic aromatic hydrocarbons; some investigations [9, 10], but not others [11, 12], report that maternal pre-pregnancy folic acid consumption may be protective. Studies have consistently reported associations between birth defects and CBTs [13, 14], and there is evidence that high birthweight (≥4,000 grams) or large-for-gestational age are associated with increased risk of CBT [15-17]. Conversely, early life allergy and asthma have been associated with reduced risk, which is hypothesized to stem from enhanced immune surveillance and elimination of malignant cells in affected individuals (although this could also be attributable to an immunosuppressive effect of the tumor itself) [18]. In many studies, findings varied by tumor subtype, timing of exposure, and timing of diagnosis.

During infancy, the developing immune system may be influenced by environmental exposures, including breastfeeding. Human milk contains immunomodulatory compounds that may influence the immune system's capacity to detect and eliminate cancerous cells. These include maternal glucocorticoids [19] with well-characterized anti-leukemic effects [20] as well as secreted antibodies, cytokines, hormones, and oligosaccharides [21]. These compounds are integral to the development of the infant's immune system and gut microbiome, and could contribute to the inverse associations between breastfeeding and immune-mediated chronic diseases [22]. However, studies of breastfeeding and CBT have produced equivocal results. Breastfeeding ≥6 months was associated with a non-significantly reduced risk of CBT in Swedish [23] (OR 0.7, 95% CI 0.4-1.3) and Australian [24] (OR 0.77, 95% CI 0.44-1.35) studies. Conversely, no association was observed between breastfeeding and CBT in the United Kingdom Childhood Cancer Study [25] (UKCCS) (OR 1.01, 95% CI 0.85-1.21) or in a pooled analysis of two nationwide French case-control studies [26] (OR 1.0, 95% CI 0.9-1.3). A systematic review and meta-analysis of five studies including N=899 childhood central nervous system tumor cases concluded that there was little evidence of an association [27].

The rarity of CBT (3-5 cases per hundred thousand children in most populations) and the heterogeneity among subtypes are significant barriers to the identification of risk factors and may partly explain the inconsistent findings in the literature. To overcome these, we pooled data from ten epidemiologic studies in the Childhood Cancer & Leukemia International Consortium (CLIC) [28]. We sought to determine whether breastfeeding is associated with CBT overall, as well as astrocytoma, medulloblastoma/PNET, and ependymoma specifically.

METHODS

Participating Studies

CLIC was established in 2007 to facilitate etiologic studies of childhood leukemia [28], and subsequently expanded its focus to include pediatric solid tumors. Currently, affiliated Principal Investigators (PIs) representing >50 epidemiologic studies performed in 19 countries contribute data to pooled analyses and meta-analyses of childhood cancer. The PIs of ten studies contributed data for the present study (**Table S1**). These included nationwide studies from France (ESCALE and ESTELLE), Germany (GCCR), Greece (NARECHEM-ST), New Zealand (NZCCS), and the United Kingdom (UKCCS), as well studies from Quebec, Texas, Washington State, and California, performed between 1974 and 2019. In the study from Washington State, breastfeeding status was ascertained by linkage between a population-based cancer registry and vital records; in other studies, mothers completed structured questionnaires that asked about breastfeeding and other exposures. Requested data included case-control status; age at diagnosis (among cases) or interview (among controls); breastfeeding status (ever/never and duration); sex; mode of delivery; birthweight; history of daycare attendance, infections, and allergy during the first year of life; and maternal age, education, and race/ethnicity. Data harmonization and analysis were performed at Baylor College of Medicine (BCM; Houston, TX USA) between October 2020 and July 2022. This study was performed in accordance with the Principles of the Declaration of Helsinki. Participating studies were approved by the relevant institutional review boards or ethics committees. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (**Table S2**)**.**

Data Harmonization

We included cases and controls 1-14 years of age at diagnosis or interview, respectively. We evaluated all childhood brain tumors (CBT) collectively and astrocytoma, medulloblastoma/primitive neuroectodermal tumor (PNET), and ependymoma individually, according to the International Classification of Childhood Cancers, Third Edition (ICCC-3) standard definitions (**Table S3**). We compared the odds of CBT among children who were ever

breastfed and breastfed ≥6 months versus never breastfed, and evaluated breastfeeding duration (in months) as a continuous variable. Except in the study from Washington State, where duration was not reported, we considered children breastfed <1 week to be never breastfed, as breastfeeding may not be fully established during the first few days of life. As duration was not measured in Washington State, we considered these children breastfed if birth records indicated the mother was breastfeeding when discharged from hospital and excluded them from analyses of breastfeeding ≥6 months and breastfeeding duration.

Statistical Analysis

Statistical analyses were performed in R v3.6.3 (R Foundation, Vienna, Austria). As the exposure of interest was breastfeeding up to 1 year of age, we excluded infants and children with missing breastfeeding data from all analyses. We summarized the distributions of demographic and breastfeeding variables by case-control status and subtype using counts and percentages, and tested for significant differences between cases and controls using X^2 tests. Thereafter, we employed two distinct analytic approaches.

First, we combined data from all participants and estimated pooled odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between breastfeeding variables and CBT/CBT subtypes using unconditional logistic regression. All models were adjusted for study, and adjusted models additionally included terms for sex and age at diagnosis/interview (i.e., the matching factors), as well as birthweight, mode of delivery (vaginal, cesarean), maternal education (secondary or less, post-secondary), maternal race/ethnicity (Hispanic, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, non-Hispanic white, or other/unknown), and maternal age at birth. Because detailed information on maternal race and ethnicity were not collected in the French ESCALE and ESTELLE studies, the race/ethnicity of subjects from these studies was classified as unknown in our primary analyses. All studies and all available controls were included in models for CBT subtypes, which were adjusted for the same covariates. Among studies that provided data (see **Table 1**), we computed models adjusted for daycare attendance and history of infections during infancy (both yes/no) to assess whether early life infectious exposures might confound associations between breastfeeding and CBT. Based on evidence that tumor immune surveillance and the impact of nutrition on the developing immune system may be sexually dimorphic [29, 30], we performed sex-specific analyses. We also performed separate analyses of children <5 and ≥5 years of age, as we hypothesized that breastfeeding may be associated with reduced odds of CBT at younger but not older ages and that mothers of younger children may recall breastfeeding practices more accurately. In each of

these, we tested for additive and multiplicative interactions based on the method proposed by Knol et al. [31] and operationalized in the 'interactionr' package [32].

Second, we estimated summary ORs and 95% CIs using random effects meta-analysis with inverse variance weighting ('metagen' function in the 'meta' package), and summarized the results in forest plots ('forest' function in the 'meta' package). The I^2 statistic was used to estimate heterogeneity (low heterogeneity: <25%; moderate heterogeneity: 25-74%; high heterogeneity: ≥75%). We used the 'InfluenceAnalysis' function in the 'dmetar' package to identify outliers and potentially influential studies per the criteria of Viechtbauer and Cheung [33]. We compared results from random effects meta-analysis of all studies to those produced by iteratively excluding one study at a time ('leave-one-out analyses').

Finally, to better understand the association of breastfeeding *per se* with CBT risk, we performed latent class analysis (LCA; R package 'poLCA') [34]. First, using the observed indicator variables of breastfeeding, mode of delivery, birthweight, daycare attendance during infancy, maternal age, and maternal education, we constructed models with a minimum of two and maximum of five latent classes and compared goodness-of-fit based on the Bayesian information criterion (BIC). Next, we estimated the OR and 95% CI of CBT and its subtypes from predicted class memberships in the model with the optimal BIC, adjusting for study, age at diagnosis/interview, and sex (i.e., a three-step approach) [35].

Table 1 Demographic Characteristics of Cases and Controls in the Pooled Study Sample, N (%).

	Controls (N=8,128)	CBT Cases (N=2,610)	Astrocytoma (N=1,092)	MB or PNET (N=695)	Ependymoma (N=263)	Other (N=560)
Sex						
Male	4,405 (54.2)	1,441 (55.2)	557 (51.0)	439 (63.2)	155 (58.9)	290 (51.8)
Female	3,723 (45.8)	1,169 (44.8)	535 (49.0)	256 (36.8)	108 (41.1)	270 (48.2)
Age (years)						
1-4	3,558 (43.8)	1,059 (40.6)	409 (37.5)	294 (42.3)	148 (56.3)	208 (37.1)
5-9	2,725 (33.5)	1,013 (38.8)	425 (38.9)	296 (42.6)	68 (25.9)	224 (40.0)
10-14	1,845 (22.7)	538 (20.6)	258 (23.6)	105 (15.1)	47 (17.9)	128 (22.9)
Birthweight (g)						
<2500	431 (5.3)	162 (6.2)	66 (6.0)	37 (5.3)	18 (6.8)	41 (7.3)
2500-3999	6,814 (83.8)	2,131 (81.6)	891 (81.6)	570 (82.0)	211 (80.2)	459 (82.0)
≥4000	857 (10.5)	301 (11.5)	133 (12.2)	82 (11.8)	32 (12.2)	54 (9.6)
Missing	26 (0.3)	16 (0.6)	2 (0.2)	6 (0.9)	2 (0.8)	6 (1.1)
Mode of delivery						
Vaginal	6,434 (79.2)	2,100 (80.5)	881 (80.7)	572 (82.3)	205 (77.9)	442 (78.9)
Cesarean	1,409 (17.3)	455 (17.4)	183 (16.8)	109 (15.7)	56 (21.3)	107 (19.1)
Missing or unknown	285 (3.5)	55 (2.1)	28 (2.6)	14 (2.0)	2 (0.8)	11 (2.0)
Daycare in infancy[1]						
No	2,483 (50.5)	798 (50.9)	308 (47.7)	275 (58.6)	76 (46.3)	139 (48.3)
Yes	2,404 (48.9)	761 (48.6)	335 (51.9)	192 (40.9)	87 (53.0)	147 (51.0)
Missing	25 (0.5)	8 (0.5)	3 (0.5)	2 (0.4)	1 (0.6)	2 (0.7)
Infections in infancy[2]						
None	1,273 (37.5)	264 (39.5)	83 (36.9)	105 (43.2)	23 (36.5)	53 (38.7)
Any (including multiple)	2,105 (62.1)	399 (59.7)	142 (63.1)	136 (56.0)	39 (61.9)	82 (59.9)
Missing	13 (0.4)	5 (0.7)	0 (0.0)	2 (0.8)	1 (1.6)	2 (1.5)
Breastfeeding						
Never	2,862 (35.2)	927 (35.5)	395 (36.2)	248 (35.7)	96 (36.5)	188 (33.6)
Ever	5,266 (64.8)	1,683 (64.5)	697 (63.8)	447 (64.3)	167 (63.5)	372 (66.4)
≥6 months	1,679 (22.7)	548 (23.2)	230 (23.1)	145 (22.3)	65 (26.6)	108 (22.7)
Maternal age (yrs)						

	Controls (N=8,128)	CBT Cases (N=2,610)	Astrocytoma (N=1,092)	MB or PNET (N=695)	Ependymoma (N=263)	Other (N=560)
<20	329 (4.0)	133 (5.1)	53 (4.9)	34 (4.9)	13 (4.9)	33 (5.9)
20-24	1,550 (19.1)	591 (22.6)	268 (24.5)	140 (20.1)	57 (21.7)	126 (22.5)
25-29	2,907 (35.8)	960 (36.8)	399 (36.5)	255 (36.7)	100 (38.0)	206 (36.8)
30-34	2,265 (27.9)	639 (24.5)	256 (23.4)	176 (25.3)	68 (25.9)	139 (24.8)
35-39	868 (10.7)	230 (8.8)	96 (8.8)	64 (9.2)	20 (7.6)	50 (8.9)
≥40	184 (2.3)	35 (1.3)	17 (1.6)	9 (1.3)	4 (1.5)	5 (0.9)
Missing or unknown	25 (0.3)	22 (0.8)	3 (0.3)	17 (2.4)	1 (0.4)	1 (0.2)
Maternal education						
Secondary or less	4,783 (58.8)	1,508 (57.8)	580 (53.1)	407 (58.6)	154 (58.6)	367 (65.5)
Tertiary/some tertiary	3,167 (39.0)	1,015 (38.9)	447 (40.9)	275 (39.6)	104 (39.5)	189 (33.8)
Missing or unknown	178 (2.2)	87 (3.3)	65 (6.0)	13 (1.9)	5 (1.9)	4 (0.7)
Maternal race/ethnicity						
Non-Hispanic White	4,609 (56.7)	1,728 (66.2)	732 (67.0)	428 (61.6)	171 (65.0)	397 (70.9)
Non-Hispanic Black	106 (1.3)	54 (2.1)	20 (1.8)	14 (2.0)	9 (3.4)	11 (2.0)
Hispanic	322 (4.0)	170 (6.5)	80 (7.3)	44 (6.3)	20 (7.6)	26 (4.6)
Asian/Pacific Islander	162 (2.0)	74 (2.8)	27 (2.5)	20 (2.9)	6 (2.3)	21 (3.8)
Other or unknown	2,929 (36.0)	584 (22.4)	233 (21.3)	189 (27.2)	57 (21.7)	105 (18.8)

Abbreviations: CBT=childhood brain tumor; MB=medulloblastoma; PNET=primitive neuroectodermal tumor.

1. Data available for children in the ESCALE/ESTELLE (France; N=3,181), NARECHEM-ST (Greece; N=398), NZCCS (New Zealand; N=322), Québec (Canada; N=531), Texas (N=129), and UKCCS (United Kingdom; N=1,885) studies. Percentages calculated based on the number of subjects with available data. In total, data on daycare attendance were available for 60.1% of controls and 59.7% of cases in the pooled study sample.

2. Data available for children in the ESCALE/ESTELLE (France; N=3,183), NARECHEM-ST (Greece; N=407), NZCCS (New Zealand; N=307) and Texas studies (N=144). In the ESCALE and ESTELLE studies, multiple infections were defined as ≥4 episodes of one type of infection, or 1-3 episodes of ≥2 types of infection during the first year of life. In NARECHEM-ST, NZCCS, and Texas, multiple infections were defined as diagnosis of more than type of infection, or multiple episodes of the same type of infection, during the first year of life. Percentages were calculated based on the number of subjects with available data. In total, data on infections during infancy were available for 41.6% of controls and 25.4% of cases.

RESULTS

Our analysis included 2,610 cases with CBT (1,092 with astrocytoma, 695 with medulloblastoma/PNET, 263 with ependymoma, and 560 with other subtypes) and 8,128 controls (**Table 1**). We observed a male preponderance among cases and, as participating studies matched on sex, among controls. Whereas the proportions of cases and controls who attended daycare during infancy were similar, we observed differences with respect to age at interview, birthweight, mode of delivery, history of infections during infancy, and maternal age, education, and race/ethnicity by case-control status (all $p<0.05$). With respect to CBT subtypes, as anticipated, we observed variation in the distributions of sex and age at diagnosis. We also observed that a smaller proportion of cases with medulloblastoma/PNET than other subtypes attended daycare during infancy, and a larger proportion of ependymoma cases were delivered by cesarean section.

When comparing across CBT subtypes, we found differences with respect to sex ratio, age at diagnosis, mode of delivery, daycare attendance during infancy, maternal age, and maternal education.

Ever breastfeeding rates among mothers of controls ranged from 49.2% (ESCALE) to 89.5% (Washington State) (**Table S4**)**.** A majority of women in all studies except NZCCS discontinued breastfeeding within 6 months. In the pooled dataset, there was no difference in the proportions of cases and controls who were ever breastfed (64.5% vs. 64.8%) or breastfed ≥6 months (23.2% vs. 22.7%). We found no association of CBT with ever breastfeeding (OR 1.04, 95% CI 0.94-1.15), breastfeeding ≥6 months (OR 1.06, 95% CI 0.93-1.22), or breastfeeding duration in months (OR 1.00, 95% CI 0.99-1.01) in pooled multivariable logistic regression models (**Table 2** and **Figure 1**). Similarly, breastfeeding was not associated with astrocytoma, medulloblastoma/PNET, or ependymoma in models stratified by subtype. We found increased ORs for ependymoma among children breastfed ≥6 months, though estimates were imprecise and all 95% CIs included unity. Meta-analysis produced similar findings (**Table 2** and **Figures S1-S3**). Heterogeneity was low ($I^2 < 25\%$) except in the analysis of breastfeeding duration and any CBT ($I^2 = 31\%$), and no studies were identified as influential. Results were unchanged in leave-one-out analyses.

Figure 1 Adjusted odds ratio and 95% confidence interval of any childhood brain tumor (N=2,610 cases), astrocytoma (N=1,092 cases), medulloblastoma or primitive neuroectodermal tumor (N=695 cases), and ependymoma (N=263) among children according to any breastfeeding (squares), breastfeeding six months or longer (triangles), and each additional

month of breastfeeding (circles) relative to never breastfeeding. Estimates were calculated in the pooled data and are adjusted for study, sex, mode of delivery, birthweight, age at diagnosis, maternal education, maternal race/ethnicity, and maternal age at birth

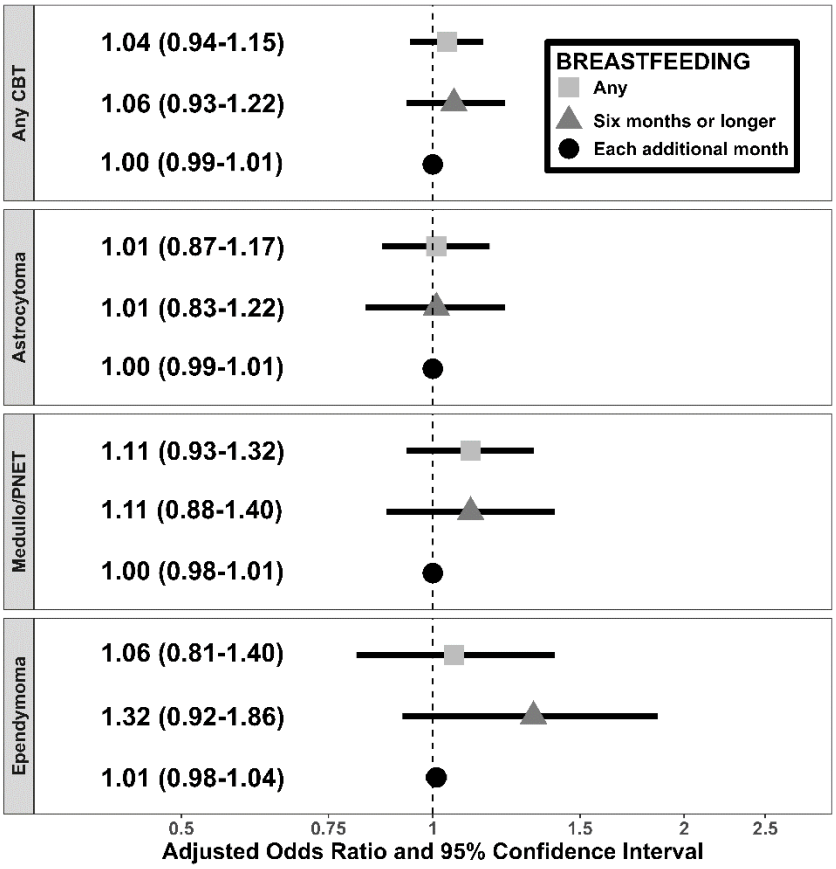

Table 2 Breastfeeding and Odds of Brain Tumors in Children ≥1 Year of Age, Pooled Dataset.

	Ever breastfed (vs. never)[4]	Breastfed ≥6 mos (vs. never)[5]	Breastfeeding (per mo increase)[5]
Any brain tumor			
Crude pooled odds ratio[1]	1.01 (0.91-1.11)	1.00 (0.88-1.14)	1.00 (0.99-1.01)
Adjusted pooled odds ratio[2]	1.04 (0.94-1.15)	1.06 (0.93-1.22)	1.00 (0.99-1.01)
Summary odds ratio from meta-analysis[3]	1.02 (0.88-1.19)	1.04 (0.83-1.29)	1.00 (0.98-1.02)
Astrocytoma			
Crude pooled odds ratio[1]	1.00 (0.87-1.15)	0.96 (0.80-1.16)	1.00 (0.98-1.01)
Adjusted pooled odds ratio[2]	1.01 (0.87-1.17)	1.01 (0.83-1.22)	1.00 (0.99-1.01)
Summary odds ratio from meta-analysis[3]	1.01 (0.85-1.19)	0.98 (0.77-1.24)	0.99 (0.97-1.02)
Medulloblastoma or PNET			
Crude pooled odds ratio[1]	1.09 (0.92-1.29)	1.06 (0.85-1.33)	1.00 (0.98-1.01)
Adjusted pooled odds ratio[2]	1.11 (0.93-1.32)	1.11 (0.88-1.40)	1.00 (0.98-1.01)
Summary odds ratio from meta-analysis[3]	1.06 (0.81-1.40)	1.09 (0.78-1.51)	1.00 (0.97-1.02)
Ependymoma			
Crude pooled odds ratio[1]	1.03 (0.79-1.34)	1.23 (0.88-1.71)	1.01 (0.98-1.03)
Adjusted pooled odds ratio[2]	1.06 (0.81-1.40)	1.32 (0.92-1.86)	1.01 (0.98-1.04)
Summary odds ratio from meta-analysis[3]	1.08 (0.74-1.58)	1.45 (0.85-2.48)	1.02 (0.98-1.06)

1. Adjusted for study.
2. Adjusted for study, sex, mode of delivery, birthweight, age at diagnosis, maternal education, maternal race/ethnicity, and maternal age at birth.
3. Summary odds ratio from random effects meta-analysis. Study-specific estimates are adjusted for factors in (2).
4. Based on data from ESCALE and ESTELLE (France), GCCR (Germany), NARECHEM-ST (Greece), NZCCS (New Zealand), Québec (Canada), Texas, UKCCS (United Kingdom), and the Washington State registry linkage study.
5. OR per one month increase in breastfeeding duration. Based on data from ESCALE and ESTELLE (France), GCCR (Germany), NARECHEM-ST (Greece), NZCCS (New Zealand), Québec (Canada), Texas, and UKCCS (United Kingdom).

Adjustment for daycare attendance during infancy (**Table S5**) or daycare attendance and history of infections during infancy (**Table S6**) did not influence our findings. For astrocytoma and medulloblastoma/PNET, we observed point estimates <1 for females but >1 for males, with significant additive interaction in the case of ever breastfeeding and astrocytoma (OR_{female} 0.88, 95% CI 0.72-1.07; OR_{male} 1.15, 95% CI 0.94-1.41) (**Table S7**). There was a tendency towards decreased odds of CBT according to breastfeeding among younger children (OR 0.87, 95% CI 0.75-1.02), whereas breastfeeding was associated with increased odds of CBT among older children (OR 1.16, 95% CI 1.02-1.32) (**Table S8**). We observed similar results for CBT subtypes.

A four-class LCA model achieved the optimal BIC. The conditional probability of breastfeeding was high in Class Two (80%) and Class Three (77%) whereas it was lower in Class One (39%) and Class Four (50%); classes differed with respect to rates of cesarean delivery, high and low birthweight, and daycare attendance during infancy as well as the distributions of maternal age and maternal education (**Table 3**). Notably, point estimates for children in Class Three were <1 for all tumor types, whereas children in Class Two appeared to be at increased odds of ependymoma (OR 2.68, 95% CI 1.20-6.00) despite similar conditional breastfeeding probabilities (**Table 4**). The odds of ependymoma also appeared to be increased for children in Class Four (OR 3.46, 95% CI 1.53-7.76), which was characterized by relatively low rates of vaginal birth, daycare attendance, and maternal post-secondary education as well as relatively high rates of high or low birthweight.

Table 3 Conditional Response Probabilities for Observed Variables in Latent Class Analysis.

	Class 1 (N=2,156)	Class 2 (N=3,311)	Class 3 (N=318)	Class 4 (N=694)
Breastfed	0.39	0.80	0.77	0.50
Mode of delivery				
Vaginal	0.91	0.36	0.85	0.44
Cesarean	0.09	0.00	0.11	0.56
Unknown	0.00	0.64	0.03	0.00
Birthweight (grams)				
<2,500	0.05	0.05	0.02	0.18
2,500-3,999	0.87	0.79	0.87	0.75
≥4,000	0.09	0.11	0.11	0.07
Unknown	0.00	0.04	0.00	0.01
Attended daycare	0.50	0.24	0.63	0.25
Maternal age (years)				
<20	0.06	0.10	0.00	0.02
20-24	0.27	0.30	0.05	0.10
25-29	0.37	0.34	0.39	0.28
30-34	0.21	0.17	0.42	0.29
35-39	0.08	0.05	0.12	0.22
≥40	0.02	0.00	0.02	0.06
Unknown	0.00	0.04	0.00	0.02
Maternal education				
Secondary or less	0.95	0.64	0.22	0.62
Post-secondary	0.05	0.35	0.78	0.37
Unknown	0.00	0.01	0.00	0.01

Includes N=4,912 controls and N=1,567 cases (646 cases with astrocytoma, 469 cases with medulloblastoma/primitive neuroectodermal tumor [PNET], and 164 cases with ependymoma) from ESCALE (France), ESTELLE (France), NARECHEM-ST (Greece), NZCCS (New Zealand), Texas (USA), UKCCS (United Kingdom), and the Quebec Registry Study (Canada).

Table 4 Odds ratio (OR) and 95% confidence interval (CI) of CBT and CBT subtypes according to latent class.

	CBT	Astrocytoma	Medulloblastoma & PNET	Ependymoma
Class 1	1.00	1.00	1.00	1.00
Class 2	0.93 (0.68-1.27)	0.65 (0.42-1.01)	1.08 (0.63-1.84)	2.68 (1.20-6.00)
Class 3	0.69 (0.33-1.49)	0.51 (0.20-1.42)	0.59 (0.16-2.38)	0.66 (0.02-7.72)
Class 4	1.09 (0.78-1.51)	1.07 (0.66-1.72)	0.91 (0.51-1.61)	3.46 (1.53-7.76)

Includes N=4,912 controls and N=1,567 cases (646 cases with astrocytoma, 469 cases with medulloblastoma/primitive neuroectodermal tumor [PNET], and 164 cases with ependymoma) from ESCALE (France), ESTELLE (France), NARECHEM-ST (Greece), NZCCS (New Zealand), Texas (USA), UKCCS (United Kingdom), and the Quebec Registry Study (Canada).

Estimates are adjusted for study, sex, and age at diagnosis (cases) or interview (controls).

DISCUSSION

Brain tumors are the most common solid tumor diagnosis in children older than one year and the leading cause of mortality due to cancer in children. Breastfeeding may reduce the risk of childhood leukemia and has been investigated in relation to CBT, though results are equivocal [27, 36]. We pooled data on >2,600 cases with CBT in the Childhood Cancer & Leukemia International Consortium in order to evaluate whether breastfeeding was associated with all CBT collectively, as well as astrocytoma, medulloblastoma and PNET, or ependymoma. Breastfeeding rates were similar among cases with CBT and controls, and we found little evidence that breastfeeding was associated with CBT or any evaluated subtype.

It has been hypothesized that infections and early life immune exposures may be involved in the etiology of CBT, though this remains unproven. Maternal infection during pregnancy has been associated with increased risk of CBT in offspring [37] and a population-based case-control study incorporating data from four European countries reported three- and four-fold increases in the odds of glioma and embryonal tumors, respectively, among children with ≥4 sick days relative to 0-1 sick days per month [38]. Conversely, some evidence has emerged that social contact, daycare attendance, and birth order may be associated with reduced risk of CBT [37, 39]. Whereas infections per se may increase risk of CBT, daycare attendance, large family size, and crowding may strengthen the immune system, enhancing immune surveillance and subsequently reducing cancer risk [37].

Breastfeeding is another immunomodulatory exposure that may modify the risk of childhood cancer [27, 36, 40]. Immunologically active agents in breast milk including secreted maternal antibodies and human milk oligosaccharides promote normal development of the immune system, reducing the risk of infections and potentially enhancing detection and elimination of cancerous cells. Despite the biologic plausibility of an association between breastfeeding and CBT, the literature is equivocal. Shaw et al. reported that the OR of CBT among breastfed children was 0.8 (95% CI 0.6-1.2) [37] and Greenop et al. reported that it was 0.81 (95% CI 0.47-1.38). Similar associations were seen for breastfeeding ≥6 months: Greenop reported an OR of 0.77 (95% CI 0.44-1.35) and Hardell et al. reported an OR of 0.7 (95% CI 0.4-1.3). A pilot study performed at two treatment centers in the United Kingdom reported a substantial decrease in the risk of CBT among breastfed children (OR 0.4, 95% CI 0.2-1.2), contrary to findings from the UKCCS (OR 1.01, 95% CI 0.85-1.21) [25]. No association between breastfeeding ≥6 months and CBT was reported in population-based case-control studies from France (OR 1.0, 95% CI 0.8-1.4) [26] or Germany (OR 0.91, 95% CI 0.66-1.25) [41]. Finally, in

the ESCALE Study, the OR of CBT among exclusively breastfed children was 1.2 (95% CI 0.9-1.6). We found little evidence of an association between breastfeeding and CBT. While the classical view of the CNS as an immune-privileged site has been revised [42, 43], it is conceivable that breast milk constituents may interact differently with CNS and peripheral immune cells, which could explain the finding that breastfeeding is associated with leukemia [27, 36, 44, 45] but not CBT despite similarities in the proposed mechanisms of association.

Breastfed and never breastfed children may have unique early life exposures. For instance, breastfeeding initiation varies by maternal race/ethnicity, age, and education, and breastfed children experience fewer infections in early life [40]. Whereas daycare attendance may be associated with a reduced risk of CBT, it may also lead to breastfeeding cessation or supplementation with formula milk or complementary foods. To address these points, we adjusted multivariable models for maternal demographic characteristics, and performed sensitivity analyses additionally including terms for daycare attendance and history of infections during infancy. Further adjustment for these factors did not alter our findings substantively.

Because sex differences in immunity and inflammation have been described and may contribute to sex ratio disparities in childhood cancer [30], we performed separate analyses among males and females. Although no breastfeeding-CBT associations were statistically significant in sex-stratified models, we observed some indications of effect modification by sex, with ORs for astrocytoma and medulloblastoma/PNET below the null among females but above the null among males. The implications of these findings are unclear; they may indicate sexual dimorphism in the relationship between breastfeeding and CBT, or may be driven by sample size.

It is possible that breastfeeding and other early life exposures would be associated with tumors diagnosed in younger but not older children, given their latency. In addition, infant feeding practices may be more accurately recalled by mothers of younger children. For these reasons, we performed analyses stratified by age at diagnosis or interview. Most commonly, breastfeeding was associated with ORs <1 for tumors diagnosed <5 years of age but >1 for tumors diagnosed ≥5 years of age. A Brain Tumor Epidemiology Consortium review highlighted the importance of timing of infectious exposures, noting that early childhood infections tended to be associated with reduced risk of CBT, whereas infections in later childhood were associated with increased risk [4]. It is also possible that sociodemographic characteristics associated with breastfeeding (lower birth order [46], older maternal age [47], greater maternal education and employment outside the home [48, 49], and maternal White or Asian/Pacific Islander race/ethnicity [50]) are themselves associated with CBT among older children [4]. In the present

study, we observed no strong associations between maternal demographic characteristics and CBT or CBT subtypes.

Using LCA, we identified two groups with similar breastfeeding rates but different distributions of maternal age and education, mode of delivery, birthweight, and daycare attendance during infancy. We found some evidence that the odds of medulloblastoma/PNET and ependymoma differed between these groups, suggesting that breastfeeding in and of itself is not associated with reduced odds of these tumors. Rather, risk may be modulated by additional sociodemographic and perinatal factors associated with breastfeeding.

Our study has several strengths. Notably, it is the largest pooled analysis and individual participant data meta-analysis of breastfeeding and CBT to date. Most published studies considered all CBT; our large sample size allowed us to evaluate major histologic subtypes individually. Studies collected detailed exposure data, thus we were able to adjust for several potential confounders and other early life infectious exposures. Several of the included case-control studies were population-based, ensuring nearly complete ascertainment of cases. Certain limitations are also noted. Except in the study from Washington State, breastfeeding practices were assessed using maternal report, and may be subject to recall and reporting bias. Although our study included data from ten studies performed in seven countries, detailed information on maternal race and ethnicity were lacking for some participants, and those for whom it was known were predominantly non-Hispanic White or European, and our results may not be generalizable to other populations. Lastly, because bias-adjusted methods for three-step latent class analysis are not widely implemented in R, we used a naïve three-step approach; it has been shown that this method may be biased towards the null owing to errors in the predicted class memberships [51].

Conclusions

Our findings from a large international pooled analysis do not suggest that breastfeeding is associated with reduced risk of childhood brain tumors. As the proportion of CBT diagnoses attributable to *de novo* or inherited genetic variations is estimated to be low, there is likely a role for environmental factors in their etiology, and future studies should evaluate other early life exposures.

DECLARATIONS

ETHICAL APPROVAL

This study was performed in accordance with the Principles of the Declaration of Helsinki. Participating studies were approved by the relevant institutional review boards or ethics committees.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

AUTHORS' CONTRIBUTIONS

Conceptualization: JMS, ER, BAM, MES. **Data curation:** JMS, EThP, AB, JDD, MK, EN, CI-R, JC, ER, EK, FE, JS, BAM, MES. **Formal analysis:** JMS. **Funding acquisition:** ER, BAM, MES. **Methodology:** JMS, EThP, AB, JDD, MK, EN, CI-R, JC PMB, RM-C, ER, FE, JS, BAM, MES. **Resources:** JMS, AB, JDD, MK, CI-R, EK, FE, BAM, MES. **Software:** JMS. **Supervision:** EThP, JDD, CI-R, JC, PMB, RM-C, ER, FE, JS, BAM, MES. **Validation:** AB, JDD, MK, EN, CI-R, FE, BAM. **Visualization:** JMS. **Writing – original draft:** JMS, ER, BAM, MES. **Writing – review and editing:** JMS, EThP, AB, JDD, MK, EN, CI-R, JC, PMB, RM-C, ER, EK, FE, JS, BAM, MES.

FUNDING

This work was directly supported by Children with Cancer UK (PGPA\100000037 to MES, ER, and BAM).

Childhood Cancer & Leukemia International Consortium (CLIC) administration, annual meetings, and pooled analyses were partially supported by the National Cancer Institute (NCI), USA (R03CA132172, Cancer Epidemiology Consortia), National Institute of Environmental Health Sciences (NIEHS), USA (P01ES018172, R01ES009137, R13ES021145, R13ES022868, R13ES024632, R13ES031473, and U13ES026496), the US Environmental Protection Agency (USEPA), USA (RD83451101), Children with Cancer UK (CwCUK), Alex's Lemonade Stand Foundation (ALSF), São Paulo Research Foundation (FAPESP), Northwestern Mutual (NM), Texas Children's Hospital (TCH), Childhood Cancer Research Fund (CCRF), and individual member study institutions.

Funding for ESCALE and ESTELLE was provided by: the Institut National de la Santé et de la Recherche Médicale (INSERM), the Institut National du Cancer (INCa), the Agence Nationale

de la Recherche (ANR; grant ID ANR-10-COHO-0009), the Fondation pour la Recherche Médicale, the French Ministère de l'Environnement, the Association pour la Recherche sur le Cancer (ARC), the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), the Agence Française de Sécurité Sanitaire de l'Environment et du Travail (AFSSET), the association Enfants et Santé, the Institut Electricité Santé, Cancéropôle Île-de-France, the Fondation de France, the Fondation Jeanne Liot, the Fondation Weisbrem-Berenson, the Ligue Contre le Cancer du Val de Marne, the association Cent pour Sang la Vie, and the Ligue Contre le Cancer. Dr. Bonaventure is supported by a fellowship from the Fondation ARC pour la Recherche sur le Cancer (PDF20190508759).

The Canadian study was funded by the National Cancer Institute of Canada (grants 014113, 010735-CERN, and RFA0405), the Medical Research Council of Canada (grant MOP 37951), the Fonds de la Recherche en Santé du Québec (grant 981141), the Canadian Bureau of Chronic Disease Epidemiology, Health and Welfare Canada, the Leukemia Research Fund of Canada, and the National Health and Research Development Program.

The German studies were supported by the German Federal Ministry for the Environment, Reactor Safety and Nature Preservation (West Germany) and the Ministry of Social Affairs of Lower Saxony.

NARECHEM-ST is supported in part by the Hellenic Society for Social Pediatrics and the National and Kapodistrian University, Athens, Greece.

The NZCCS was funded by the Health Research Council of NZ, the NZ Lottery Grants Board, the Otago Medical School (Faculty Bequest Funds), the Cancer Society of NZ, the Otago Medical Research Foundation, and the A.B. de Lautour Charitable Trust.

The United Kingdom Childhood Cancer Study (UKCCS) is sponsored and administered by Leukaemia and Lymphoma Research.

The WCCBT Study was supported by the United States National Cancer Institute (CA47082) and was part of an international collaborative effort coordinated by the International Agency for Research on Cancer's Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) Program.

AVAILABILITY OF DATA AND MATERIALS

The underlying data are subject to data use agreements that prohibit us from sharing them publicly. They may be obtained by application to the participating Principal Investigators.

CONSENT TO PARTICIPATE

Participants or their legal guardians provided written informed consent at the time of primary data collection.

CONSENT TO PUBLISH

Study participants provided written informed consent and/or verbal assent for the publication of data at the time of data collection.

REFERENCES

1. Curtin SC, Minino AM, Anderson RN (2016) Declines in cancer death rates among children and adolescents in the united states, 1999-2014. NCHS data brief: 1-8. https://doi.org/
2. Pollack IF, Jakacki RI (2011) Childhood brain tumors: Epidemiology, current management and future directions. Nat Rev Neurol 7: 495-506. https://doi.org/10.1038/nrneurol.2011.110
3. Udaka YT, Packer RJ (2018) Pediatric brain tumors. Neurol Clin 36: 533-56. https://doi.org/10.1016/j.ncl.2018.04.009
4. Johnson KJ, Cullen J, Barnholtz-Sloan JS, et al. (2014) Childhood brain tumor epidemiology: A brain tumor epidemiology consortium review. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 23: 2716-36. https://doi.org/10.1158/1055-9965.EPI-14-0207
5. Adel Fahmideh M, Scheurer ME (2021) Pediatric brain tumors: Descriptive epidemiology, risk factors, and future directions. Cancer Epidemiol Biomarkers Prev 30: 813-21. https://doi.org/10.1158/1055-9965.Epi-20-1443
6. Bondy ML, Lustbader ED, Buffler PA, Schull WJ, Hardy RJ, Strong LC (1991) Genetic epidemiology of childhood brain tumors. Genet Epidemiol 8: 253-67. https://doi.org/10.1002/gepi.1370080406
7. Hemminki K, Kyyrönen P, Vaittinen P (1999) Parental age as a risk factor of childhood leukemia and brain cancer in offspring. Epidemiology 10: 271-5.
8. Johnson KJ, Carozza SE, Chow EJ, et al. (2009) Parental age and risk of childhood cancer: A pooled analysis. Epidemiology 20: 475-83. https://doi.org/10.1097/EDE.0b013e3181a5a332
9. Bunin GR, Gallagher PR, Rorke-Adams LB, Robison LL, Cnaan A (2006) Maternal supplement, micronutrient, and cured meat intake during pregnancy and risk of medulloblastoma during childhood: A children's oncology group study. Cancer Epidemiol Biomarkers Prev 15: 1660-7. https://doi.org/10.1158/1055-9965.Epi-06-0254
10. Milne E, Greenop KR, Bower C, et al. (2012) Maternal use of folic acid and other supplements and risk of childhood brain tumors. Cancer Epidemiol Biomarkers Prev 21: 1933-41. https://doi.org/10.1158/1055-9965.epi-12-0803
11. Schüz J, Weihkopf T, Kaatsch P (2007) Medication use during pregnancy and the risk of childhood cancer in the offspring. Eur J Pediatr 166: 433-41. https://doi.org/10.1007/s00431-006-0401-z
12. Stålberg K, Haglund B, Strömberg B, Kieler H (2010) Prenatal exposure to medicines and the risk of childhood brain tumor. Cancer Epidemiol 34: 400-4. https://doi.org/10.1016/j.canep.2010.04.018
13. Norwood MS, Lupo PJ, Chow EJ, et al. (2017) Childhood cancer risk in those with chromosomal and non-chromosomal congenital anomalies in washington state: 1984-2013. PLoS One 12: e0179006. https://doi.org/10.1371/journal.pone.0179006
14. Lupo PJ, Schraw JM, Desrosiers TA, et al. (2019) Association between birth defects and cancer risk among children and adolescents in a population-based assessment of 10 million live births. JAMA oncology 5: 1150-8. https://doi.org/10.1001/jamaoncol.2019.1215
15. Adel Fahmideh M, Peckham-Gregory EC, Schraw JM, et al. (2021) Maternal and perinatal factors are associated with risk of pediatric central nervous system tumors and poorer survival after diagnosis. Sci Rep 11: 10410. https://doi.org/10.1038/s41598-021-88385-3
16. Bjorge T, Sorensen HT, Grotmol T, et al. (2013) Fetal growth and childhood cancer: A population-based study. Pediatrics 132: e1265-75. https://doi.org/10.1542/peds.2013-1317

17. Dahlhaus A, Prengel P, Spector L, Pieper D (2017) Birth weight and subsequent risk of childhood primary brain tumors: An updated meta-analysis. Pediatr Blood Cancer 64. https://doi.org/10.1002/pbc.26299
18. Shu X, Prochazka M, Lannering B, et al. (2014) Atopic conditions and brain tumor risk in children and adolescents--an international case-control study (cefalo). Ann Oncol 25: 902-8. https://doi.org/10.1093/annonc/mdu048
19. Hollanders JJ, Heijboer AC, van der Voorn B, Rotteveel J, Finken MJJ (2017) Nutritional programming by glucocorticoids in breast milk: Targets, mechanisms and possible implications. Best Pract Res Clin Endocrinol Metab 31: 397-408. https://doi.org/10.1016/j.beem.2017.10.001
20. Teuffel O, Kuster SP, Hunger SP, et al. (2011) Dexamethasone versus prednisone for induction therapy in childhood acute lymphoblastic leukemia: A systematic review and meta-analysis. Leukemia 25: 1232-8. https://doi.org/10.1038/leu.2011.84
21. Cacho NT, Lawrence RM (2017) Innate immunity and breast milk. Front Immunol 8: 584-. https://doi.org/10.3389/fimmu.2017.00584
22. Dawod B, Marshall JS, Azad MB (2021) Breastfeeding and the developmental origins of mucosal immunity: How human milk shapes the innate and adaptive mucosal immune systems. Curr Opin Gastroenterol 37: 547-56. https://doi.org/10.1097/mog.0000000000000778
23. Hardell L, Dreifaldt AC (2001) Breast-feeding duration and the risk of malignant diseases in childhood in sweden. Eur J Clin Nutr 55: 179-85. https://doi.org/10.1038/sj.ejcn.1601142
24. Greenop KR, Bailey HD, Miller M, et al. (2015) Breastfeeding and nutrition to 2 years of age and risk of childhood acute lymphoblastic leukemia and brain tumors. Nutr Cancer: 1-11. https://doi.org/10.1080/01635581.2015.998839
25. Harding NJ, Birch JM, Hepworth SJ, McKinney PA (2007) Breastfeeding and risk of childhood cns tumours. Br J Cancer 96: 815-7. https://doi.org/10.1038/sj.bjc.6603638
26. Bailey HD, Rios P, Lacour B, et al. (2017) Factors related to pregnancy and birth and the risk of childhood brain tumours: The estelle and escale studies (sfce, france). Int J Cancer 140: 1757-69. https://doi.org/10.1002/ijc.30597
27. Martin RM, Gunnell D, Owen CG, Smith GD (2005) Breast-feeding and childhood cancer: A systematic review with metaanalysis. Int J Cancer 117: 1020-31. https://doi.org/10.1002/ijc.21274
28. Metayer C, Milne E, Clavel J, et al. (2013) The childhood leukemia international consortium. Cancer Epidemiol 37: 336-47. https://doi.org/10.1016/j.canep.2012.12.011
29. Klein SL, Flanagan KL (2016) Sex differences in immune responses. Nat Rev Immunol 16: 626-38. https://doi.org/10.1038/nri.2016.90
30. Dorak MT, Karpuzoglu E (2012) Gender differences in cancer susceptibility: An inadequately addressed issue. Frontiers in Genetics 3. https://doi.org/10.3389/fgene.2012.00268
31. Knol MJ, VanderWeele TJ (2012) Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol 41: 514-20. https://doi.org/10.1093/ije/dyr218
32. Alli BY (2021) Interactionr: An r package for full reporting of effect modification and interaction. Software Impacts 10: 100147. https://doi.org/https://doi.org/10.1016/j.simpa.2021.100147
33. Viechtbauer W, Cheung MW (2010) Outlier and influence diagnostics for meta-analysis. Res Synth Methods 1: 112-25. https://doi.org/10.1002/jrsm.11
34. Linzer DA, Lewis JB (2011) Polca: An r package for polytomous variable latent class analysis. Journal of Statistical Software 42: 1 - 29. https://doi.org/10.18637/jss.v042.i10
35. Bakk Z, Kuha J (2021) Relating latent class membership to external variables: An overview. Br J Math Stat Psychol 74: 340-62. https://doi.org/10.1111/bmsp.12227
36. Schraw JM, Bailey HD, Bonaventure A, et al. (2022) Infant feeding practices and childhood acute leukemia: Findings from the childhood cancer & leukemia international consortium. Int J Cancer. https://doi.org/10.1002/ijc.34062

37. Shaw AK, Li P, Infante-Rivard C (2006) Early infection and risk of childhood brain tumors (canada). Cancer Causes Control 17: 1267-74. https://doi.org/10.1007/s10552-006-0066-y
38. Andersen TV, Schmidt LS, Poulsen AH, et al. (2013) Patterns of exposure to infectious diseases and social contacts in early life and risk of brain tumours in children and adolescents: An international case-control study (cefalo). Br J Cancer 108: 2346-53. https://doi.org/10.1038/bjc.2013.201
39. Harding NJ, Birch JM, Hepworth SJ, McKinney PA (2009) Infectious exposure in the first year of life and risk of central nervous system tumors in children: Analysis of day care, social contact, and overcrowding. Cancer Causes Control 20: 129-36. https://doi.org/10.1007/s10552-008-9224-8
40. Pediatrics AAo (2012) Breastfeeding and the use of human milk. Pediatrics 129: e827-41. https://doi.org/10.1542/peds.2011-3552
41. Schüz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J (2001) Risk factors for pediatric tumors of the central nervous system: Results from a german population-based case-control study. Med Pediatr Oncol 36: 274-82. https://doi.org/10.1002/1096-911x(20010201)36:2<274::Aid-mpo1065>3.0.Co;2-d
42. Engelhardt B, Vajkoczy P, Weller RO (2017) The movers and shapers in immune privilege of the cns. Nat Immunol 18: 123-31. https://doi.org/10.1038/ni.3666
43. Forrester JV, McMenamin PG, Dando SJ (2018) Cns infection and immune privilege. Nat Rev Neurosci 19: 655-71. https://doi.org/10.1038/s41583-018-0070-8
44. Su Q, Sun X, Zhu L, et al. (2021) Breastfeeding and the risk of childhood cancer: A systematic review and dose-response meta-analysis. BMC Med 19: 90. https://doi.org/10.1186/s12916-021-01950-5
45. Kwan ML, Buffler PA, Abrams B, Kiley VA (2004) Breastfeeding and the risk of childhood leukemia: A meta-analysis. Public Health Rep 119: 521-35. https://doi.org/10.1016/j.phr.2004.09.002
46. Buckles K, Kolka S (2014) Prenatal investments, breastfeeding, and birth order. Soc Sci Med 118: 66-70. https://doi.org/10.1016/j.socscimed.2014.07.055
47. Biro MA, Yelland JS, Brown SJ (2014) Why are young women less likely to breastfeed? Evidence from an australian population-based survey. Birth. https://doi.org/10.1111/birt.12112
48. Pitonyak JS, Jessop AB, Pontiggia L, Crivelli-Kovach A (2015) Life course factors associated with initiation and continuation of exclusive breastfeeding. Maternal and child health journal. https://doi.org/10.1007/s10995-015-1823-x
49. Ogbuanu C, Glover S, Probst J, Liu J, Hussey J (2011) The effect of maternity leave length and time of return to work on breastfeeding. Pediatrics 127: e1414-27. https://doi.org/10.1542/peds.2010-0459
50. Beauregard JL, Hamner HC, Chen J, Avila-Rodriguez W, Elam-Evans LD, Perrine CG (2019) Racial disparities in breastfeeding initiation and duration among us infants born in 2015. Morbidity and Mortality Weekly Report 68: 745.
51. Bolck A, Croon M, Hagenaars J (2004) Estimating latent structure models with categorical variables: One-step versus three-step estimators. Political Analysis 12: 3-27.