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Maternal Folate Intake and Risk of Childhood Brain and Spinal Cord Tumors: A Systematic Review and Meta-Analysis

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Keywords

Central nervous system neoplasms · Prenatal nutritional physiological phenomena · Folic acid/administration and dosage · Child · Meta-analysis as topic

Abstract

Background: Many epidemiological studies have investigated the effect of maternal diet and prenatal multivitamin supplementation on pediatric cancer risk. Childhood brain and spinal cord tumors (CBSCT) have been attributed to different possible risk factors. ***Methods:*** We conducted a systematic review and meta-analysis on maternal folate intake before and during pregnancy and the risk of CBSCT. We systematically reviewed publications obtained by searching the Insitute for Scientific Information Web of Knowledge and PubMed literature databases. We extracted the risk estimate of the highest and the lowest reported categories of intake from each study and conducted a meta-analysis using a random-effects model. ***Results:*** The results of the pooled analysis of all 10 studies, 1 cohort and 9 case-control studies, indicated that maternal folate intake was inversely associated with CBSCT risk (OR 0.77; 95% CI 0.67–0.88, $p < 0.001$; $I^2 = 51.22\%$, $p = 0.001$). Separate analyses on the basis of the source of folate (folic acid supplementation, dietary folate) and in relation to the timing of exposure (before pregnancy, during pregnancy) found that folic acid supplementation was associated with an approximately 23% reduction in CBSCT risk (OR 0.77, 95% CI 0.66–0.90, $p = 0.001$; $I^2 = 53.18\%$, $p = 0.001$) and consumption during pregnancy was associated with an approximately 20% reduction in CBSCT risk (OR 0.80, 95% CI 0.67–0.97, $p = 0.020$; $I^2 = 62.48\%$, $p < 0{\cdot}001$). ***Conclusions:*** Maternal consumption of folic acid is associated with a reduced risk of CBSCT. Further investigations are necessary to increase the reliability of the results and estimate the relationship between dose-response and the best outcome.

Introduction

Childhood brain and spinal cord tumors (CBSCT) are characterized by a variety of histopathological and molecular features [1]. The main cell types in the central nervous system (CNS) are neurons and glia, which arise in the early development from the primitive neuroectoderm

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[2]. CBSCT are classified in the International Classification of Childhood Cancer (ICCC-3) among which astrocytomas represent the most frequent type of CBSCT, followed by intracranial and intraspinal embryonal tumors, other gliomas and ependymomas and choroid plexus tumors [3, 4].

CNS and miscellaneous intracranial and intraspinal neoplasms are the most common form of solid tumors in children (0–14 years) and represent the leading cause of cancer mortality in this age-group [5]. In the United States, the overall annual average age-adjusted incidence rate for 2010–2014 for CBSCT was 4.89 (95% IC 4.83–4.96) per 100,000 population for children and adolescents (0–19 years) and 4.75 (95% IC 4.67–4.83) per 100,000 population for children [5]. The 5-year relative survival rate for the CBSCT in the United States during 2007 through 2013 was 72.5% for children (0–14 years) and 78.9% for adolescents (15–19 years) [6]. Despite the effort to identify the etiology of CNS and miscellaneous intracranial and intraspinal neoplasms, the confirmed risk factors are solely ionizing radiation [7] and selected genetic syndromes (tuberous sclerosis, neurofibromatosis 1 and 2 and Li-Fraumeni cancer family syndrome) [8], while there is ongoing debate over the possible role played by exposure to other risk factors in onset and progression of CBSCT, such as N-nitroso compounds [9], pesticides [10], tobacco [11], electromagnetic fields [12], parental occupation [13], maternal medications use [14, 15], alcohol intake [16], and breastfeeding [17].

The evidence of a possible association between the maternal folic acid intake during pregnancy and neural tube defects has been described in the scientific literature for more than 3 decades [18]. Therefore, the current WHO recommendation is to provide daily supplementation with 400 μg folic acid to women before and during pregnancy [19]. In addition, a potential beneficial effect of folic-acid containing multivitamin supplementation on other maternal and infant outcomes has been largely investigated [20, 21]. Due to its key role in DNA synthesis and repair, and gene methylation, a chemioprotective effect of folic acid against carcinogenesis is biologically plausible [22]. Synthetic folic acid showed a significantly higher bioavailability than food folate [23], although the different bioavailability from supplemental folic acid and the less ready absorption in the human digestive tract, dietary folate may also be inversely associated with risk of CBSCT [24, 25].

A reduction in pediatric cancers incidence rates after folic acid food fortification has been reported; however, the impact on incidence of CNS and miscellaneous intracranial and intraspinal neoplasms remains controversial [15, 26–28]. Several studies have previously reported an inverse association between maternal folic acid supplementation in the periconceptional period and risk of CBSCT [29–32], whereas others have reported largely null findings [33–38]. Therefore, the aim of this study was to conduct a systematic review and meta-analysis on maternal folate intake before and during pregnancy and the risk of CBSCT.

Materials and Methods

Search Strategy

Our literature search was aimed at identifying available research studies that examined the effects of maternal folic acid intake on CBSCT. We identified the studies included in our meta-analysis by searching, without restrictions, multiple literature databases including Web of Knowledge and PubMed, and selecting all the articles published up to 27th November 2017. We searched for abstracts and articles including the following terms: (folate OR "folic acid") AND (cancer OR neoplasm OR "neoplastic disease" OR tumor OR tumour OR medulloblastoma) AND (child OR pediatric OR childhood OR children) AND (brain OR "nervous system"). In addition, we supplemented this research by checking the references cited in retrieved papers and recent reviews.

Data collection

We systematically reviewed and selected the studies meeting the following criteria of eligibility: (i) assessed maternal folate intake; (ii) used a cohort, case-control, or nested case-control study design; and (iii) reported a risk estimate (hazard ratio, relative risk or OR) for CBSCT as well as its 95% CI. When studies reported data from the same population, only the most comprehensive study was enrolled. Studies providing insufficient or overlapping data were excluded. Two investigators reviewed the eligibility of all studies according to the predetermined selection criteria independently. We extracted information about study characteristics (study name, authors, publication year, study design), study population characteristics, exposure assessment, timing of exposure, sources of folate, outcomes, and variables of adjustment. The outcome of interest in our analysis was childhood brain tumors, classified according to the ICCC-3 [3]. From the enrolled studies [29–38], we derived the risk estimate of the highest relative to the lowest folate intake for the analysis.

Quality Evaluation

We used the Newcastle-Ottawa Scale Assessment [39] for the quality evaluation of the enrolled studies. Newcastle-Ottawa Scale adopted a star system scoring from 0 to 9 and a total score ≥7 indicated a high-quality study. Two investigators (G.N. and M.C.) performed the quality evaluation of each selected study and disagreements were settled by a joint re-evaluation of the original article with a third reviewer. No study was excluded on the basis of these quality criteria, in order to avoid selection bias.

Statistical Analysis

We evaluated the association between maternal folate intake and CBSCT using the statistical program ProMeta version 3.0 (IDo Statistics-Internovi, Cesena, Italy). In our selection, 9 studies reported OR [29–36, 38] and one study reported the hazard ratio [37]. For the overall estimation, the hazard ratio was taken as an approximation to the OR, and the meta-analysis was performed as if all types of ratio were ORs. The combined risk estimate was calculated using a random-effects model in which the effect measures were ORs or hazard ratio. Our analysis included data from both maternal dietary folate intake and folic acid supplementation and data regarding folate consumption both preconceptionally and during pregnancy, as independent populations.

We assessed heterogeneity between studies by the Cochran's Q statistic (χ^2), deeming $p < 0.05$ as significant, and I^2 test, which yields results ranged from 0 to 100% (I^2 = 0–25%, no heterogeneity; I^2 = 25–50%, moderate heterogeneity; I^2 = 50–75%, large heterogeneity; and I^2 = 75–100%, extreme heterogeneity) [40, 41]. To explore the sources of heterogeneity among studies and test the robustness of the associations, we conducted subgroup analyses and several sensitivity analyses. We further examined the influence of individual studies on the overall risk estimate, which was investigated by recalculating the pooled estimates for the remainder of the studies by omitting one study at each turn.

Publication bias was evaluated using the methods of Begg and Mazumdar [42] and Egger et al. [43], which both test for funnel plot asymmetry, the former based on the rank correlation between the effect estimates and their sampling variances, and the latter on the basis of a linear regression of a standard normal deviate on its precision. If the intercept of Egger's regression line deviated from zero with a p value <0.10, the funnel plot was considered asymmetrical. In case of a small number (25 or fewer) of studies enrolled in the meta-analysis, as in the current review, this test for asymmetry possesses relatively low power to detect a real publication bias. If a potential bias was detected, sensitivity analyses were performed to assess the robustness of our findings. p values reported are from 2-sided statistical tests and differences with $p < 0.05$ were considered significant.

This review is reported according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [44] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [45].

Results

Literature Search

Our initial research returned 201 citations and the flowchart of the study selection process is shown in Figure 1. After excluding 31 duplicates, the analysis of titles and abstracts identified 13 studies on maternal folate intake and CBSCT. Through the reference lists of recent relevant reviews and already selected articles, 5 additional articles were included for the analysis. From the 18 potentially eligible articles, 8 studies were excluded from the analysis after the full-text assessment, as follows (Fig. 1):

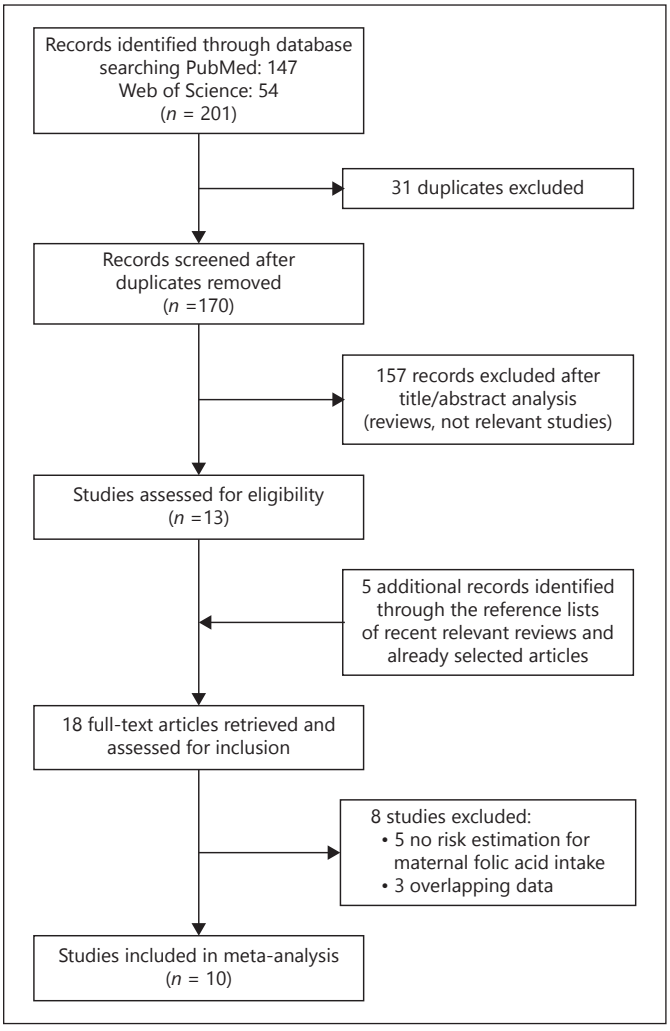

Fig. 1. Study profile.

– Five were case–control studies not reporting the risk estimate for CBSCT in relation to maternal folic acid intake [15, 46–49];

– Three were case–control studies reporting overlapping data [50–52].

Therefore, only 10 studies met the inclusion criteria: nine were case–control design studies [29–36, 38] and one was a cohort study [37] (Fig. 1).

Study Characteristics

The detailed characteristics of included studies are summarized in Table 1.

Among the studies, one considered folate supplements only [31] and 2 considered dietary folate intake only [29, 30], while the other 7 studies considered both folate supplements and dietary folate intake [32–38].

Table 1. Studies included in the meta-analysis

Authors, year, location	Type of study, population in study	Starting time		Subgroups	Dose	OR or HR	95% CI	*p* for Trend	Adjustement factors	NOS score
Bailey et al. [38], 2017 France	Case-control Children 0–15 years 301 cases/1,421 controls					CNS and miscellaneous intracranial and intraspinal neoplasms (III)			Sex, age, maternal age group, urban status of the area of residence	8
		Before pregnancy		Dietary folate intake		1.00	Ref.			
				With supplement		0.80	0.50–1.40			
					<400 µg	1.10	0.10–11.40			
					≥400 µg	1.00	0.50–2.20			
		Before or during pregnancy	Any time in pregnancy	Dietary folate intake		1.00	Ref.			
				With supplement		1.60	1.20–2.20			
					<400 µg	2.90	1.70–5.20			
					≥400 µg	1.20	0.70–2.10			
			Preconception	With supplement		0.90	0.50–1.50			
			1st trimester			1.70	1.10–2.40			
			2nd/3rd trimester			1.60	1.10–2.40			
Mortensen et al. [37], 2016 Norway	Cohort Children born 01/01/1999–31/12/2010 Cohort: 687,406 Cases: 799	Before or during pregnancy				CNS and miscellaneous intracranial and intraspinal neoplasms (III)			Birth order, smoking, maternal and paternal age, maternal and paternal education	8
				Dietary folate intake		1.00	Ref.	0.320		
				With supplement	200 µg	1.08	0.60–1.94			
					400 µg	1.18	0.78–1.78			
					600 µg	0.68	0.42–1.10			
						Astrocytoma (IIIb)				
				Dietary folate intake		1.00	Ref.	0.970		
				With supplement	200 µg	1.57	0.72–3.40			
					400 µg	1.31	0.70–2.45			
					600 µg	0.86	0.43–1.73			
						Intracranial and intraspinal embryonal tumours (IIIc)				
				Dietary folate intake		1.00	Ref.	0.690		
				With supplement	200 µg	0.61	0.14–2.59			
					400 µg	1.28	0.60–2.76			
					600 µg	0.69	0.27–1.74			
Greenop et al. [36], 2014 Australia	Case–control Children 0–15 years 293 cases/ 726 controls					CNS and miscellaneous intracranial and intraspinal neoplasms (III)				8
		Before pregnancy		Diet/supplement	≤448.57 µg	1.00	Ref.	0.070	Child's age, child's sex, child's state of residence, child's year of birth, best parental education, child's ethnicity, maternal supplement with folic acid 3 months before or during pregnancy, maternal supplement with B6/B12 3 mo before or during pregnancy, maternal consumption of alcohol during pregnancy	
					448.57–561.35 µg	0.96	0.68–1.36			
					>561.35 µg	0.70	0.48–1.02			

Table 1. (continued)

Authors, year, location	Type of study, population in study	Starting time		Subgroups	Dose	OR or HR	95% CI	*p* for Trend	Adjustement factors	NOS score
		During pregnancy		Dietary folate intake	≤448.57 µg	1.00	Ref.	0.390	Child's age, child's sex, child's state of residence, child's year of birth, best parental education, child's ethnicity, maternal consumption of alcohol during pregnancy	
					448.57–561.35 µg	0.96	0.51–1.81			
					>561.35 µg	0.72	0.33–1.55			
				With supplement	≤448.57 µg	1.00	Ref.	0.090		
					448.57–561.35 µg	0.98	0.64–1.51			
					>561.35 µg	0.67	0.42–1.06			
Milne et al. [32], 2012 Australia	Case–control Children 0–14 years 335 cases/1,363 controls					CNS and miscellaneous intracranial and intraspinal neoplasms (III)			Age, sex, state of residence, ethnicity, maternal age group, child's year of birth group, maternal education level, data source	7
		Before pregnancy		Dietary folate intake		1.00	Ref.			
				With supplement		0.55	0.32–0.93			
					0.1–300 µg	1.01	0.62–1.65	0.010		
					300.1–450 µg	0.49	0.28–0.85			
					>450.1 µg	0.60	0.38–0.98			
					per 100 µg	0.93	0.88–0.99			
		During pregnancy	1st trimester	Dietary folate intake		1.00	Ref.			
				With supplement		0.83	0.56–1.24			
					0.1–300 µg	1.05	0.70–1.60	0.030		
					300.1–450 µg	0.82	0.55–1.23			
					>450.1 µg	0.67	0.44–1.00			
					per 100 µg	0.95	0.91–1.00			
			2nd/3rd trimester	Dietary folate intake		1.00	Ref.			
				With supplement		0.87	0.54–1.39			
					0.1–300 µg	0.92	0.62–1.37	0.080		
					300.1–450 µg	0.74	0.46–1.19			
					>450.1 µg	0.68	0.43–1.09			
					per 100 µg	0.94	0.89–0.99			
						Low-grade gliomas (IIId)				
		Before pregnancy		Dietary folate intake		1.00	Ref.	<0.010		
				With supplement		0.64	0.38–1.08			
					0.1–300 µg	1.18	0.64–2.18			
					300.1–450 µg	0.42	0.20–0.89			
					>450.1 µg	0.44	0.22–0.89			
					per 100 µg	0.92	0.84–1.00			

Table 1. (continued)

Authors, year, location	Type of study, population in study	Starting time		Subgroups	Dose	OR or HR	95% CI	*p* for Trend	Adjustement factors	NOS score
		During pregnancy	1st trimester	Dietary folate intake		1.00	Ref.	0.010		
				With supplement		0.74	0.47–1.15			
					0.1–300 μg	1.11	0.65–1.89			
					300.1–450 μg	0.63	0.36–1.10			
					>450.1 μg	0.57	0.33–1.00			
					per 100 μg	0.94	0.88–1.00			
			2nd/3rd trimester	Dietary folate intake		1.00	Ref.	0.120		
				With supplement		0.73	0.46–1.17			
					0.1–300 μg	0.82	0.48–1.40			
					300.1–450 μg	0.71	0.37–1.35			
					>450.1 μg	0.63	0.34–1.17			
					per 100 μg	0.94	0.87–1.01			
									Medulloblastoma/Primitive neuroectodermal tumors of brain (IIIc*)	
		Before pregnancy		Dietary folate intake		1.00	Ref.	0.580		
				With supplement		0.71	0.33–1.52			
					0.1–300 μg	0.70	0.25–1.98			
					300.1–450 μg	0.63	0.23–1.69			
					>450.1 μg	0.80	0.31–2.02			
					per 100 μg	0.93	0.82–1.06			
		During pregnancy	1st trimester	Dietary folate intake		1.00	Ref.	0.570		
				With supplement		0.89	0.48–1.67			
					0.1–300 μg	0.84	0.36–1.95			
					300.1–450 μg	1.08	0.53–2.20			
					>450.1 μg	0.73	0.34–1.57			
					per 100 μg	0.96	0.89–1.05			
			2nd/3rd trimester	Dietary folate intake		1.00	Ref.	0.440		
				With supplement		0.87	0.45–1.71			
					0.1–300 μg	1.04	0.49–2.22			
					300.1–450 μg	0.68	0.27–1.70			
					>450.1 μg	0.81	0.33–1.95			
					per 100 μg	0.94	0.84–1.05			

* Missing atypical teratoid/rhabdoid tumors (n.3) and medulloepithelioma

Table 1. (continued)

Authors, year, location	Type of study, population in study	Starting time		Subgroups	Dose	OR or HR	95% CI	*p* for Trend	Adjustement factors	NOS score
Ortega-García et al. [35], 2010 Spain	Case-control Children 0–15 years 67 cases/155 controls					CNS and miscellaneous intracranial and intraspinal neoplasms (III)			Age, sex, socioeconomic status, associated familial syndrome, cancer in first degree relative, mother's and father's smoking habits during pregnancy, smokers fetus (overall exposure to tobacco during intrauterine period), exposure to traffic contaminants, and multivitamin intake	7
		Before pregnancy		Dietary folate intake		1.00	Ref.			
				With supplement	≥400 µg	0.34	0.10–1.06			
		During pregnancy		Dietary folate intake		1.00	Ref.			
				With supplement	≥400 µg	0.94	0.78–1.14			
Stålberg et al. [34], 2010 Sweden	Case-control Childern 0–15 years 512 cases/525 controls	Before or during pregnancy				CNS and miscellaneous intracranial and intraspinal neoplasms (III)			Maternal age at birth, parity, mother's country of birth, and level of hospital	8
				Dietary folate intake		1.00	Ref.			
				With supplement		0.60	0.30–1.10			
Bunin et al. [33], 2006 North America	Case-control Children 0–6 years 315 cases/315 controls					Medulloblastoma/Primitive neuroectodermal tumors of brain (IIIc*)			Mother's race, date of interview, child's age at interview, income, number of cigarettes smoked per day, total calories, maternal weight gain (yes/no) because of pregnancy nausea/vomiting	6
		Before pregnancy		Dietary folate intake	<267 µg	1.00	Ref.	0.650		
					267–322 µg	1.10	0.70–1.90			
					323–379	1.00	0.60–1.70			
					≥380	1.20	0.70–2.00			
				With supplement	<286 µg	1.00	Ref.	0.007		
					286–347 µg	0.90	0.50–1.50			
					348–482 µg	1.30	0.80–2.20			
					≥483 µg	0.50	0.30–0.90			
		During pregnancy	2nd trimester	Dietary folate intake		1.00	Ref.			
				With supplement		1.10	0.40–3.20	0.860		
				Dietary folate intake	<279 µg	1.00	Ref.	0.670		
					279–332 µg	1.30	0.70–2.10			
					333–403 µg	1.00	0.60–1.80			
					≥404 µg	1.00	0.60–1.60			
				With supplement	<961 µg	1.00	Ref.	0.330		
					961–1,276 µg	0.70	0.40–1.10			
					1,277–1,364 µg	0.90	0.50–1.50			
					≥1365 µg	0.80	0.50–1.30			
		* Missing atypical teratoid/rhabdoid tumors and medulloepithelioma								
Preston-Martin et al. [31], 1998	Case-control Children <5 years 372 cases/579 controls					CNS and miscellaneous intracranial and intraspinal neoplasms (III)			Centre, sex, age group	8

Table 1. (continued)

Authors, year, location	Type of study, population in study	Starting time	Subgroups	Dose	OR or HR	95% CI	*p* for Trend	Adjustement factors	NOS score
Multisite (Paris – France, Milan – Italy, Valencia – Spain, Israel, Winnipeg – Canada, Los Angeles, San Francisco, Seattle – US, Sidney – Australia		During pregnancy	With supplement	0 μg	1.00	Ref.	0.002		
				<313 μg	0.60	0.30–1.10			
				<400 μg	0.60	0.30–1.30			
				≥400 μg	0.50	0.30–0.80			
Bunin et al. [30], 1994 North America	Case-control Children 0–6 years 315 cases/315 controls				Astrocytoma (IIIb)			Income level	7
		During pregnancy	Dietary folate intake	1 quartile (low)	1.00	Ref.	0.580		
				2 quartile	0.60	0.30–1.30			
				3 quartile	1.00	0.50–2.00			
				4 quartile (high)	1.00	0.50–2.10			
					Primitive neuroectodermal tumors of brain (IIIc**)				
		During pregnancy	Dietary folate intake	1 quartile (low)	1.00	Ref.	0.003		
				2 quartile	0.70	0.30–1.30			
				3 quartile	0.60	0.30–1.10			
				4 quartile (high)	0.40	0.20–0.70			
Bunin et al. [29], 1993 North America	Case-control Children 0–6 years 166 cases/166 controls				Primitive neuroectodermal tumors of brain (IIIc**)			Factors related to the child (sex, birth order, birth weight, and duration of breast-feeding), maternal factors (age, history of miscarriage, month of prenatal visit, educational level, and income level), exposure during pregnancy (use of cigarettes, alcoholic beverages, well water, bottled water, and electric blanket or electrically heated water bed), duration of nausea that interfered with eating normally, and child's diet in the first year of life (use of multivitamin supplements and frequency of consumption of orange juice, apple juice, other fruit juice and fruit)	6
		During pregnancy	Dietary folate intake	1 quartile (low)	1.00	Ref.	0.005		
				2 quartile	0.61	0.33–1.13			
				3 quartile	0.61	0.33–1.14			
				4 quartile (high)	0.38	0.20–0.73			
					Astrocytoma (IIIb)				
		During pregnancy	Dietary folate intake	1 quartile (low)	1.00	Ref.	0.96		
				2 quartile	0.85	0.46–1.55			
				3 quartile	0.93	0.49–1.78			
				4 quartile (high)	0.95	0.51–1.76			

** Missing medulloblastoma, atypical teratoid/rhabdoid tumors and medulloepithelioma

Table 2. Results of stratified analysis of the CBSCT risk estimates for the highest compared with the lowest maternal folic acid intake[1]

	Combined risk estimate		Test of heterogeneity			Publication bias	
	value (95% CI)	*p* value	Q (%)	I^2 (%)	*p* value	Egger's test, *p* value	Begg's test, *p* value
Overall analysis (*n* = 32)[2]	0.77 (0.67–0.88)	<0.001	63.55	51.22	0.001	0.036	0.339
CNS and miscellaneous intracranial and intraspinal neoplasms (*n* = 16)	0.82 (0.68–0.99)	0.040	40.13	62.62	<0.001	0.213	0.558
Intracranial and intraspinal embryonal tumors (*n* = 10)	0.70 (0.54–0.90)	0.006	14.48	37.84	0.106	0.537	0.421
Astrocytoma (*n* = 3)	0.93 (0.63–1.38)	0.734	0.09	0.00	0.955	0.986	0.602
Low-grade glioma (*n* = 3)	0.55 (0.39–0.79)	0.001	0.59	0.00	0.743	0.511	0.602
Dietary folate intake (*n* = 7)	0.76 (0.53–1.07)	0.119	13.57	55.79	0.035	0.345	0.176
CNS and miscellaneous intracranial and intraspinal neoplasms (*n* = 1)	–	–	–	–	–	–	–
Intracranial and intraspinal embryonal tumors (*n* = 4)	0.67 (0.38–1.20)	0.178	12.48	75.95	0.006	0.063	0.174
With folic acid supplement (*n* = 24)	0.77 (0.66–0.90)	0.001	49.12	53.18	0.001	0.051	0.457
CNS and miscellaneous intracranial and intraspinal neoplasms (*n* = 14)	0.83 (0.67-1.03)	0.091	38.53	66.25	<0.001	0.249	0.381
Intracranial and intraspinal embryonal tumors (*n* = 6)	0.69 (0.52–0.91)	0.010	1.93	0.00	0.859	0.676	0.851
Before pregnancy (*n* = 9)	0.71 (0.56–0.89)	0.003	10.79	25.86	0.214	0.631	0.532
With folic acid supplement (*n* = 7)	0.64 (0.50–0.81)	<0.001	6.14	2.32	0.407	0.784	0.453
Dietary folate intake (*n* = 1)	–	–	–	–	–	–	–
During pregnancy (*n* = 19)	0.80 (0.67–0.97)	0.020	47.98	62.48	<0.001	0.132	0.278
With folic acid supplement (*n* = 13)	0.85 (0.68–1.05)	0.131	34.75	65.46	0.001	0.332	0.583
Dietary folate intake (*n* = 6)	0.69 (0.48–1.01)	0.053	10.40	51.94	0.065	0.589	0.188

[1] The risk estimates were calculated using the random-effects model.
[2] Number of data used to calculate the risk.
CBSCT, childhood brain and spinal cord tumors; CNS, central nervous system.

Five studies reported maternal folate intake during pregnancy only [29–31, 34, 37], whereas the other 5 studies presented findings for maternal folate intake before and during pregnancy separately [32, 33, 35, 36, 38].

In the selected studies, the evaluated outcomes were CBSCT and/or subgroups of CBSCT. More specifically, data were available for CBSCT from 7 studies [31, 32, 34–38], for astrocytomas from 3 studies [29, 30, 37], for the combination of medulloblastoma and primitive neuroectodermal tumor (PNET) from 2 studies [32, 33], for PNET from 2 studies [29, 30], for intracranial and intraspinal embryonal tumors from one study [37], and for low-grade glioma from one study [32] (Table 1).

Four studies were conducted in Europe (in particular, one was conducted in France [38], one in Norway [37], one in Sweden [34] and one in Spain [35]), 3 studies in North America [29, 30, 33], 2 studies in Australia [32, 36], and the remaining one was a multisite study [31].

Four studies reported tumors occurred in children aged 0–15 years [34–36, 38], 3 studies tumors occurred in children aged 0–6 years [29, 30, 33], one study considered tumors occurred in children aged less than 5 years [31], one study tumors occurred in children aged 0–14 years [32], while the cohort study evaluated risk of CBSCT in children among all live births from 1 January 1999 through 31 December 2010 [37].

Quality Assessment

Study-specific quality scores of each study are summarized in online supplemental Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000490249). The quality scores varied in the range from 6 to 8 (median: 7.5). High-quality studies (i.e., those studies that had a score ≥7) included the cohort study [37] and 7 case-control studies [30–32, 34–36, 38].

Meta-Analyses

The overall analysis of the 10 studies pooled together (*n* = 32) yielded a combined risk estimate for CBSCT of 0.77 (95% CI 0.67–0.88; $p < 0.001$) and the test of heterogeneity resulted slightly more than moderate ($I^2 = 51.22\%$, $p = 0.001$; Table 2).

We categorized the outcomes as CNS and miscellaneous intracranial and intraspinal neoplasms for the studies reporting a risk estimation for CBSCT, and as intracranial and intraspinal embryonal tumors for studies

reporting a risk estimation for intracranial and intraspinal embryonal tumors or medulloblastoma/PNET or PNET. According to the ICCC-3 classification, astrocytomas and low-grade gliomas have been categorized separately. The overall analysis stratified by the outcomes reported a significant protective effect of maternal folate intake for CNS and miscellaneous intracranial and intraspinal neoplasms, with a risk estimate of 0.82 (95% CI 0.68–0.99; $p = 0.040$), and for intracranial and intraspinal embryonal tumors with a risk estimate of 0.70 (95% CI 0.54–0.90; $p = 0.006$). The analysis showed a significantly reduced risk of incidence for low-grade gliomas (0.55; 95% CI 0.39–0.79; $p = 0.001$), although it should be noticed that it was performed on data collected from the sole study reporting this outcome [32] (Table 2).

Furthermore, we separately analyzed the results of the enrolled studies according to the source of folate (folic acid supplementation, dietary folate) in relation to the timing of exposure (before pregnancy, during pregnancy) and cancer types (CNS and miscellaneous intracranial and intraspinal neoplasms, intracranial and intraspinal embryonal tumors) in relation to the source of folate (folic acid supplementation, dietary folate). The data were stratified by source of folic acid and by timing of consumption. The forest plots are reported in Figure 2. Considering the source of folic acid, the protective effect of maternal dietary folate intake is not statistically significant (0.76; 95% CI 0.53–1.07; $p = 0.119$), while acid folic supplementation showed a statistically significant protective effect, a risk estimate of 0.77 (95% CI 0.66–0.90; $p = 0.001$). When stratifying by outcome, folate supplementation significantly reduced the risk of intracranial and intraspinal embryonal tumors by 31% (0.69; 95% CI 0.52–0.91; $p = 0.010$; Table 2).

Analyzing for the starting time of consumption, maternal folate intake before pregnancy resulted associated to a statistically significant reduction of 29% of CBSCT risk (0.71; 95% CI 0.56–0.89; $p = 0.003$), in particular the risk estimate for preconceptionally folate supplementation resulted in 0.64 (95% CI 0.50–0.81; $p < 0.001$). Moreover, maternal folate intake during pregnancy showed a statistically significant reduction (20%) of CBSCT risk, with a risk estimate of 0.80 (95% CI 0.67–0.97; $p = 0.020$); no significant effect resulted after stratifying for source of folic acid (Table 2).

The results of both heterogeneity and publication bias tests are shown in Table 2. Considerably, a significant heterogeneity was observed in the overall analysis for CBSCT ($I^2 = 51.22\%$; $p = 0.001$), and in the analyses of the effect of maternal folate intake on CNS and miscellaneous intracranial and intraspinal neoplasms ($I^2 = 62.62\%$; $p < 0.001$), of the overall effect of maternal folate supplementation ($I^2 = 53.18\%$; $p = 0.001$), and of the overall effect of maternal folate intake during pregnancy ($I^2 = 62.48\%$; $p < 0.001$; Table 2).

Publication Bias

In the overall analysis, the risk assessment for publication bias revealed a significant effect ($p = 0.036$) in Egger's test [43], while no bias ($p = 0.339$) was detected by the Begg and Mazumdar method [42]. No publication bias was detected for the other performed analyses.

Sensitivity Analyses

Sensitivity analyses investigating the influence of each single study on the overall risk estimate by omitting 1 study in turn suggested that the results were not substantially modified by any single study. In particular, the risk estimate ranged from 0.70 (95% CI 0.63–0.79, $p < 0.001$) omitting the study of Bailey et al. [38] to 0.81 (95% CI 0.69–0.96, $p = 0.017$) omitting the study of Milne et al. [32]. Of note, the heterogeneity was greatly reduced by omitting the study of Bailey et al. [38] ($I^2 = 17.28$, $p = 0.213$). In addition, exclusion of the study of Ortega-Garcia et al. [35], which caused asymmetry of the funnel plot, yielded a risk estimate of 0.76 (95% CI 0.66–0.88, $p < 0.001$) without publication bias as evidenced by both Egger's regression ($p = 0.125$) and Begg's rank correlation ($p = 0.669$).

Discussion

Several epidemiological studies have investigated the effect of maternal diet and prenatal multivitamin supplementation on pediatric cancer risk [53, 54]. The possible risk factors for the onset and progression of CBSCT have been examined in many studies, however the etiology continues to be largely unknown [55, 56]. Several studies have recently suggested a potential protective effect of folic acid on certain pediatric cancers [53, 57, 58], while only a minority of studies investigated the effects of maternal folate intake on CBSCT [29–38].

To the best of our knowledge, this is the first systematic review and meta-analysis that estimates the inverse association between maternal folate intake and CBSCT, which represents an important issue of public health. This association was found to be significant only in half of the selected studies. Considering the heterogeneity of the population in each of the studies, data collection, year of study, the evaluated outcomes, and to the variety of

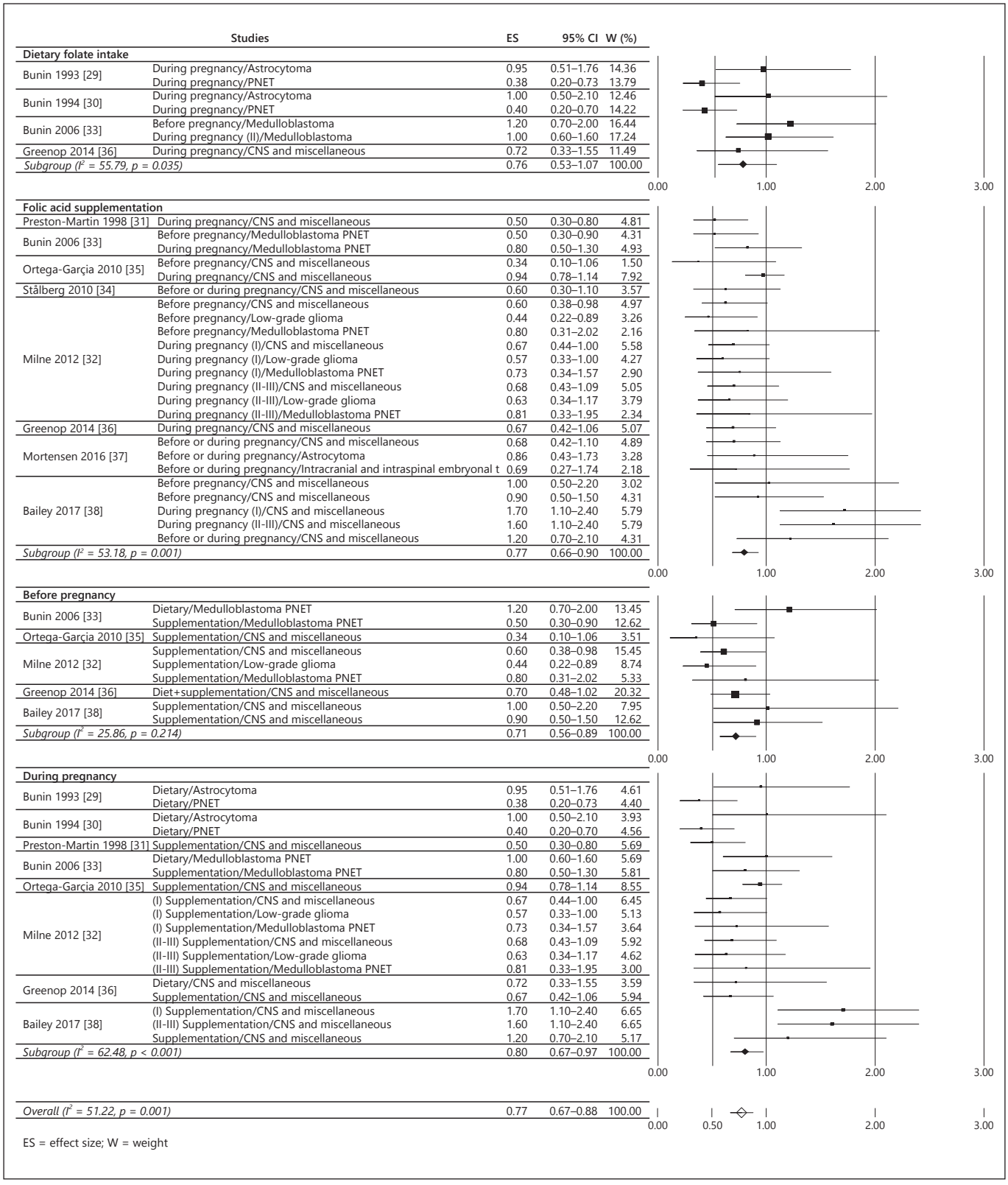

Fig. 2. Effect of maternal folate intake of CBSCT. Dietary folate intake, folic acid supplementation, before pregnancy, and during pregnancy.

strategies in maternal folate supplementation, none of these factors could exhaustively explain the difference in the results. However, our meta-analysis suggests that maternal folate intake reduces significantly the risk of CBSCT and in particular, when the highest versus the lowest intake values were compared, maternal folate intake resulted in a significant reduction of CBSCT risk (OR 0.77; 95% CI 0.67–0.88; $p < 0.001$), whether the consumption started preconceptionally (OR 0.71; 95% CI 0.56–0.89; $p = 0.003$) or during pregnancy (OR 0.80; 95% CI 0.67–0.97; $p = 0.020$). Stratifying data by the source of folate (diet and supplementation), the analysis also showed a protective effect; particularly, folate supplementation resulted in a significantly reduced risk of CBSCT (OR 0.77; 95% CI 0.66–0.90; $p = 0.001$). The results of our study have confirmed the role of folate in preventing carcinogenesis [29–32]. Folates are a group of hydrosoluble B vitamins, present at high concentration in green leafy vegetables. Humans are unable to synthetize folates de novo, hence it is of crucial importance to assume folate either directly with the diet or through microbial breakdown during digestion. In fact, folate plays an important role in the maintenance of the DNA stability through the regulation of DNA biosynthesis, repair, and methylation.

Furthermore, folate has garnered much attention because of its purported role in the pathogenesis of neural tube defects and adverse pregnancy outcomes [18, 59–61]. Although the appreciation of the role of folate in carcinogenesis is a recent development, folate deficiency has been implicated in the development of several human epithelial cell cancers, such as cervical, colorectal, lung, and esophageal cancer, and many others [22, 62–65]. Thus, considering the preventive effect of folate on neural tube defects, on other maternal and infant outcomes, and CBSCT, it is important to reinforce WHO recommendation of folic acid consumption before and during pregnancy and to improve the level of adherence to this recommendation.

We are aware that our study has important limitations. The main limitation of this meta-analysis is the inclusion of only a small number of studies estimating the association between maternal folate intake and CBSCT. In this study, the data were included after a comprehensive search of the published literature, but the analysis remained limited because there were only 7 studies reporting the specific amount of maternal folate intake [31–33, 35–38]. The other reports included in the present meta-analysis did not calculate the specific amount of maternal folate intake in the diet or with the supplement but instead considered only the consumption [29–30, 34]. Maternal folate intake varies considerably within studies, and this represents a possible explanation for the heterogeneity across studies. The outcome estimates were taken from published data; therefore, systematic biases could not be minimized and the data in some cases were incomplete. Hence in some subgroup analyses, the numbers of included studies were too small and may influence the conclusions. Since the included studies in our meta-analysis were almost all case-control studies [29–36, 38] and only one a cohort study [37], recall bias and selection bias could have restricted the precision of our results. The preventive effect suggested by the case-control studies may be due to potential confounding factors and exposure misclassification. Thus, our results should be interpreted with caution.

Further investigations that study the dietary and supplemental maternal folate intake in different periods of pregnancy (preconceptionally, 1st trimester, 2nd trimester, 3rd trimester) are needed to increase the reliability of the results and estimate the relationship between dose-response and the best outcome.

Conclusions

The present meta-analysis provides evidence in support of the association between maternal folate intake and reduced risk of CBSCT. Our results reinforce WHO recommendation of folic acid consumption before and during pregnancy and the importance to improve the level of adherence to this intervention. Further studies are needed to clarify these discrepancies, to support these findings on different populations, and to investigate more accurately both the dose–response effects and the relationship between starting time of folic consumption in pregnancy and best outcome.

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Ethics Statement

Ethical approval was not required for this study.

Disclosure Statement

No potential conflicts of interest were disclosed.

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