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Review Article

The association between birth weight and the risk of neuroblastoma: a meta-analysis of observational studies involving 4,361,141 participants

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Abstract: One of the most common extracranial solid tumors in childhood is neuroblastoma. In this study, it was aimed to perform a systematic review and meta-analysis to evaluate the risk of neuroblastoma in both high and low birth weights. The PRISMA and MOOSE guidelines were followed during the design, analysis, and reporting of this study. A comprehensive literature search was undertaken for the published papers in Embase, PubMed/Medline, Scopus, and the Web of Science (WoS) databases. The odds ratio (OR) of neuroblastoma in high and low birth weight groups, with 95% confidence intervals (CIs), were calculated using the random-effects and fixed-effects models. A total of 16 papers and 4,361,141 participants were included in this study. When the random-effects model and the fixed-effects model were used, high birth weight was associated with an increased risk of neuroblastoma (OR = 1.17; 95% CI: 1.06-1.29, P = 0.002; heterogeneity: Chi^2 = 2.33, df = 15, I^2 = 0%, P>0.05). Similarly, it was observed that individuals with low birth weights may also face an increased risk of developing neuroblastoma later in life (OR = 1.19; 95% CI: 1.03-1.37, P = 0.017; heterogeneity: Chi^2 = 16.93, df = 15, I^2 = 0%, P = 0.323). In conclusion, both high and low birth weight in individuals may be among the important risk factors for neuroblastoma development.

Keywords: Neuroblastoma, meta-analysis, birth weight

Introduction

One of the most common extracranial childhood solid tumors is neuroblastoma [1]. It develops from embryonic neural crest tissue and contributes to around 15% of all pediatric cancer fatalities. The incidence rate is 107 cases per 1,000,000 individuals aged 0-14 years [1, 2]. Because of its unexpected biological activity, which varies from spontaneous remission to highly quick metastatic spread and making detection, therapy, and prognosis difficult, it has been labeled a "clinical enigma" of cancer research [3].

A definitive risk factor for neuroblastoma has yet to be discovered. Since neuroblastoma occurs in the beginning of life, it has been hypothesized that prenatal risk factors may play an important role in the development of this disease. However, in few studies conducted so far, it has been reported that several factors such as maternal smoking [4], maternal medications [5], or supplements taken during pregnancy [6], may affect the development of the disease.

Considering all this, it is considered as an alternative approach to concentrate on exposure indicators, which can be easily collected in large samples with low bias and are well-established markers of the intrauterine environment. Birth weight is one such marker as it is taken immediately after birth by experienced individuals with low systematic error and is usually documented in medical records [7]. Studies have

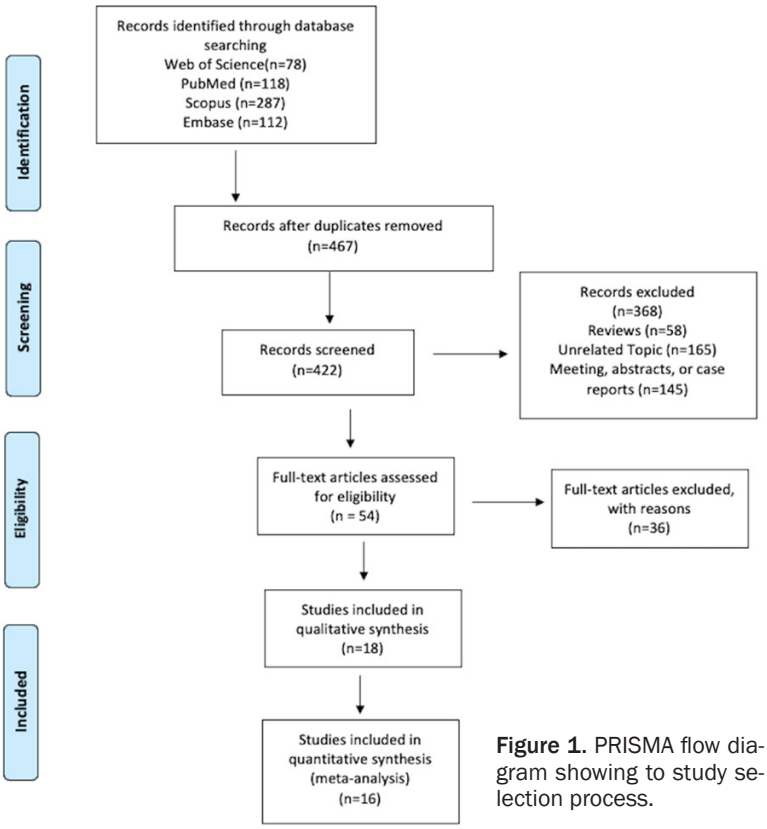

Figure 1. PRISMA flow diagram showing to study selection process.

reported that external conditions such as nutrition during pregnancy and maternal diseases are important in terms of birth weight [8, 9]. The effect of birth weight in newborns and children with neuroblastoma has been previously reviewed in various studies [10-13]. In this study, we aimed to evaluate the association between birth weight and neuroblastoma risk with a meta-analysis.

Methods

Literature search and search strategy

"Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)" [14] and "Meta-analysis of Observational Studies in Epidemiology (MOOSE)" [15] reporting guidelines were closely followed during the reporting, design, and analysis of this study. Between February-April (2023), structured and comprehensive literature searches were conducted for the published papers in Web of Science, PubMed/Medline, Scopus, and Embase databases, and an update was performed on July 28 for this search. Related four major factors were considered for the search query lines when choosing the keywords: "birth weight", "neuroblastoma", "prenatal", "birth characteristics". The related keywords were combined using Medical Subject Headings (MeSH) and text terms, and the Boolean operators (AND/OR) were used to integrate the keywords. Search strategies in the related literature are available in Table S1. A flow-chart demonstrating the selection process is also presented in **Figure 1**. Relevant studies that could be included in the meta-analysis were downloaded from related databases. Afterward, these studies were transferred to Mendeley data management program for data evaluation and analysis. The study protocol is registered in PROSPERO with ID number CRD42021274163.

Study selection and inclusion/exclusion criteria

Original case-control or cohort studies published about the effect of birth weight and risk of neuroblastoma were included in this meta-analysis. Studies that were published in the English language were researched, and no other types of paper were examined. In addition, studies covering the following criteria listed below were included in this research: i) being an original study examining the relationship between birth weight and neuroblastoma risk, and ii) odds ratio (OR) with 95% CIs for risk of neuroblastoma in at least two strata of birth weight had to be reported. Exclusion criteria: i) reviews, guidelines, opinions, or other non-original data publications; ii) projects and clinical trials that were incomplete; and iii) no clinical evidence from animal and laboratory studies.

Data extraction and acquisition, and quality assessment

Papers were initially searched based on the title and abstract in related database, and the

full text of the appropriate papers were examined. The article titles and abstracts, and any differences amongst co-authors regarding which papers were eligible and which were not were handled using Delphi consensus criteria were examined by two independent investigators (MEA and HE) [16], and the data was extracted into a pre-defined spreadsheet created using Microsoft Excel®. The following study characteristics were extracted: "publication year", "country", "region", "study design", "year of birth", "age at diagnosis", "study size", "matching ratio (if case-control study)", "matching variables (if case-control study)", "source of controls (if case-control study)", "source of case diagnosis", "source of data for birth weight", "effect measures" and "confounders". Primary outcomes were defined as the relationship between low birth weight and high birth weight and neuroblastoma. Secondary outcomes included subgroup analyses. All data entries were validated by an independent reviewer. To overcome data limitations - in case of missing data or doubt - the corresponding author(s) of the articles were contacted via email to obtain more details. Prepared data were cross-checked by two investigators via a standard spreadsheet to reach consensus. Quality assessment for each study was performed using the Newcastle-Ottawa Scale (NOS) (Table S2) [39].

Statistical analysis

Forest plots were utilized to compute and graphically illustrate the OR with 95% CI of both high and low birth weight, and to summarize them. Three different meta-analytical methodologies were associated with the study in conducting the meta-analysis: 1) 4000 g was taken as the limit to assess neuroblastoma risk below and above 4000 g for dichotomous comparison; 2) for low birth weight, 2500 g was taken as the cut-off point; and 3) for trend analysis, the regression coefficients obtained from the study were combined with the pool-first method [17]. We estimated the neuroblastoma risk above and below the threshold value, with crude OR and 95% CI, with dual assessments.

We used the "pool-first method" to measure the dose-response association between birth weight and neuroblastoma risk in studies with more than two categories of birth weight. Greenland and Longnecker [17] proposed this approach, which permits meta-analytic pooling of regression data while accounting for the fact that estimates used to generate single regression coefficients are linked within one research. This problem is handled by pooling the data inside each study ("pool first") to acquire the relevant regression coefficients for each research, and then pooling these regression coefficients. The resultant pooled regression coefficient can be viewed similarly to a single study's regression coefficient. A U-shaped relationship between birth weight and the risk of neuroblastoma was discovered by visually inspecting the plots of 15 of the 16 independent studies. A log-quadratic model was used to construct a study-specific linear and quadratic regression coefficient, as well as 95% CI, for each of these investigations. To use a random-effects model, the resultant linear and quadratic regression coefficients and their 95% CIs were pooled using the pool-first strategy [17]. We replicated the pool-first analysis after doing the sensitivity analyses, this time using a linear model confined to the birth-weight spectrum and studies that used registries to gather birth-weight data.

Cochran's Q test and I^2 statistics, as developed by Higgins et al. [18], was used to quantified between-study heterogeneity in all meta-analyses. A ratio of more than 50% in I^2 statistics and a $P \leq 0.05$ in Cochran's Q test revealed that significant heterogeneity [18]. The analyses were carried out using both random-effect and fixed-effect models. Sensitivity analyses - "all studies were excluded from analysis separately" - were conducted to test the reliability of the study results. To investigate probable sources of variability between research outcomes, four distinct subgroup analyses were conducted. To begin, we produced separate estimates for all research conducted in North America (The United States and Canada) and those conducted in Europe. Next, we divided all research into two groups based on how they obtained birth weight (registry/certificate vs. interview). Then, subgroup estimates were produced based on how the case diagnosis was obtained (registry vs. others). Finally, we divided all the research into two groups based on the source of controls (registry/certificate vs. others). For each significant outcome in our research, Egger's linear regression test and

Table 1. Distribution of included studies by country, design, birth year(s), diagnosis year(s), age at diagnosis (years), and number of cases/controls

Study (First author (year))	Country	Design	Birth year(s)	Diagnosis year(s)	Diagnosis age (years)	Number of cases/controls
Bjorge (2008) [25]	Norway	Cohort	1967-2004	1967-2004	0-15	Cohort: 2,127,452
Bluhm (2008) [26]	Sweden	Case-control	1973-95	1973-95	NA	245/1,225
Buck (2001) [10]	USA	Case-control	1971-87	1976-87	0-5	310/155
Chow (2007) [27]	USA	Case-control	1980-2004	1980-2004	NA	240/2,400
Hamrick (2001) [28]	USA, Canada	Case-control	1974-94	1992-94	0-18	504/504
Johnson and Spitz (1985) [23]	USA	Case-control	1949-78	1964-78	0-14	157/314
Johnson (2008) [29]	USA	Case-control	1976-2004	1988-2004	0-14	155/8.752
McLaughlin (2008) [11]	USA	Case-control	1983-2001	1985-2001	0-14	529/12,010
Munzer (2008) [12]	France	Case-control	1989-2004	2003-04	0-14	191/1,681
Neglia (1988) [24]	USA	Case-control	NA	NA	0-9	97/388
O'Neill (2015) [22]	USA	Case-control	1970-2004	1980-2004	0-14	16,554/53,716
O'Neill (2015) [22]	UK	Case-control	1980-2007	1980-2007	0-14	23,772/33,206
Parodi (2014) [30]	Italy	Case-control	1998-2001	1998-2001	0-10	153/1,044
Rios (2016) [31]	France	Case-control	NA	2003-2004-2010-2011	0-15	357/1,783
Schuz (1999) [32]	Germany	Case-control	1978-94	1992-94	0-14	183/1,785
Uruyama (2007) [13]	USA	Case-control	1983-97	1988-97	0-4	508/1,015
Heck (2020) [33]	Taiwan	Cohort	2004-2014	2004-2014	0-14	Cohort: 2,079,037

NA: not available.

funnel plots were utilized to examine the possibility of publication bias. The statistical significance level was determined as a 2-sided P<0.05. All analyses were performed using ProMeta3® meta-analysis software [19].

Results

In the initial search, a total of 595 articles were found in related databases (with 78 in Web of Science, 118 in PubMed, 112 in Embase, and 287 in Scopus). After a preliminary review and the elimination of duplicates, 467 papers were screened and chosen for further evaluation. A total of 18 studies were included in this study after applying the inclusion/exclusion criteria. Only an adjusted OR for neuroblastoma following high birth weight was reported in one research [20] and an unadjusted OR could not be determined from the data. Another study [21] had to be removed due to significant case overlap with a prior study. In one paper [22], since both USA and UK data were reported, it was assumed that this research represents separate studies in the quantitative analysis. In addition, since only low birth weight OR was reported in one study [23] and only high birth weight OR was also reported in one study [24], the relevant studies were added to the analyses separately. As a result, a total of 16 papers (**Figure 1**) could be used for meta-analysis [10-13, 22-33]. The major parameters of the included studies are available in **Tables 1**, **2**. It was observed that the studies were generally of high quality in the quality assessment (Table S2).

A total of 4,361,141 participants were involved in the research, two of the 16 studies were cohort, and the other 14 studies used a case-control strategy with matching ratios ranging from 1:1 to 1:10 in case-control studies. The initial research came out in 1985, and the most current one came out in 2020. The research was carried out in the "United States, Canada, France, Norway, Sweden, Italy, Taiwan and Germany". Participants varied in age from 0 to 18. The number of participants in the study ranged from 471 to 2,127,452. Cases came from cancer registries in ten of the investigations, whereas they came from other sources in the other six.

High birth weight and neuroblastoma risk

There were 15 studies [10-13, 22, 24-33] that provided data for calculating the OR (95% CI) of risk of neuroblastoma in patients with a high birth weight (>4000 g) compared to those with lower birth weight. The forest plot with ORs with 95% CIs, as well as the pooled estimate for the risk of neuroblastoma in high birth weight par-

Table 2. Descriptive and clinical features of included studies in the meta-analysis

Study (First author)	Source of controls	Source of case diagnosis	Source of data for birth weight	Original study results
Bjorge (2008) [25]	NA (cohort: population)	Cancer registry	Birth registry	"Unadjusted risk ratio (95% CI) for birth weight 4000-4499 g (vs. 3000-3499 g): 1.4 (0.9-2.1); for birth weight <2500 g: 0.6 (0.2-1.9)"
Bluhm (2008) [26]	Birth registry	Swedish Cancer Register or Death Register	National Cancer Register	"OR (95% CI), adjusted for birth year, for birth weight >4500 g (vs. 2500-4499 g): 1.07 (0.53-2.18); for birth weight <2500 g: 1.05 (0.51-2.19)"
Buck (2001) [10]	Birth registry	Cancer registry	Birth certificates	"Unadjusted OR (95% CI) for birth weight >4000 g (vs. 3000-3499 g): 1.2 (0.6-2.2); for birth weight <2500 g: 0.9 (0.4-2.2)"
Chow (2007) [27]	Birth certificates	Cancer registry	Birth certificates	"OR (95% CI), adjusted for birth year, for birth weight >4000 g (vs. 2500-3999 g): 1.25 (0.87-1.79); for birth weight <2500 g: 0.75 (0.38-1.51)"
Hamrick (2001) [28]	Random digit dialing	Clinical records[a]	Interview	"OR (95% CI), adjusted for gender, race, maternal education, and household income, for birth weight 4001-4499 g (vs. 2501-4000 g): 1.1 (0.7-1.7); for birth weight 1500-2500 g: 1.1 (0.6-2.0)"
Johnson and Spitz (1985) [23]	Birth certificates	Death certificates	Birth certificates	"Unadjusted OR (95% CI) for birth weight <2500 g (vs. 4380 g): 3.22 (1.13-9.20)"
Johnson (2008) [29]	Birth registry	Cancer surveillance	Birth records	"Hazard ratio (95% CI), adjusted for sex and birth year, for birth weight 4000 g (vs. 2500-4000 g): 1.10 (0.70-1.73); for birth weight <2500 g: 1.17 (0.60-2.28)"
McLaughlin (2008) [11]	Birth certificates	Cancer registry	Birth certificates	"Risk ratio (95% CI), adjusted for birth year, region, gender, and race, for birth weight 44500 g (vs. 2500-3499 g): 1.4 (0.7-2.5); for birth weight <2500 g: 1.5 (1.0-2.1)"
Munzer (2008) [12]	Random digit dialing	Cancer registry	Interview	"OR (95% CI), adjusted for age and gender, for birth weight 4000 g (vs. 3000-3499 g): 1.6 (0.9-2.8); for birth weight <2500 g: 1.8 (0.8-3.8)"
Neglia (1988) [24]	Birth certificates	Clinical records	Birth certificates	"Unadjusted OR (95% CI) for birth weight 4000 g (vs. <4000 g): 0.96 (0.47-1.73)"
O'Neill (2015) [22]	Birth records	Cancer registry	Birth certificates	"OR adjusted for gestational age, birth order, plurality, maternal age, and race/ethnicity for birth weight >4000 g (vs. 3000-3999): 1.22 (1.02-1.45); for birth weight <2500: 1.36 (0.96-1.93)-1.14 (0.87-1.51)"
O'Neill (2015) [22]	Birth records	National Cancer Register	Birth records	"OR adjusted sex, period, and region of birth for birth weight >4000 g (vs. 3000-3999): 1.27 (0.94-1.71); for birth weight <2500: 1.31 (0.61-2.78)-0.98 (0.58-1.64)"
Parodi (2014) [30]	Birth certificates	Clinical records	Interview	"OR (95% CI), adjusted for birth year, for birth weight >4000 g: 1.1 (0.57-2.00); for birth weight <2500 g: 0.59 (0.22-1.6)"
Rios (2016) [31]	Random digit dialing	Clinical records	Birth records	"OR (95% CI), adjusted for age and sex, birth-order, maternal age, urban status of the area of residence and study birth weight 4000 g (vs. 3000-3499 g): 1.4 (0.9-2.2); for birth weight <2500 g: 1.2 (0.9-1.7)"
Schuz (1999) [32]	Population	Cancer registry	Interview	"OR (95% CI), adjusted for socio-economic status, for birth weight 4000 g (vs. 2500-4000 g): 1.3 (0.8-2.1); for birth weight <2500 g: 2.4 (1.2-4.8)"
Uruyama (2007) [13]	Birth registry	Cancer registry	Birth certificates	"Unadjusted OR (95% CI) for birth weight (term) 4000 g (vs. 2500-4000 g): 1.25 (0.88-1.78); for birth weight <2500 g (term): 1.40 (0.65-3.04)"
Heck (2020) [33]	NA (cohort: population)	National Cancer Register	Birth registry	"HR (95% CI) Adjusted mother's age, father's age, family income, for birth weight >4000 g (vs. 2500-3999 g): 0.77 (0.25-2.42); for birth weight <2500 g: 0.79 (0.42-1.45)"

NA: not available. [a]Cases came from two collaborative clinical trial groups.

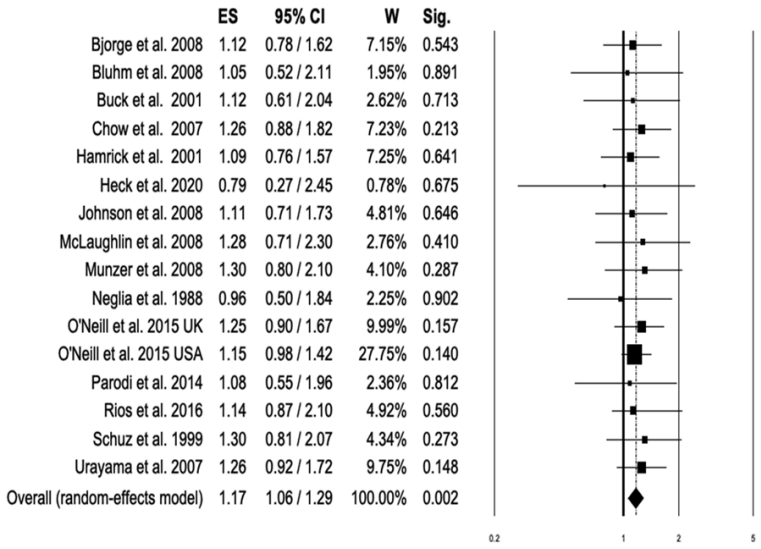

Figure 2. ORs for neuroblastoma in participants with high birth weight (>4000).

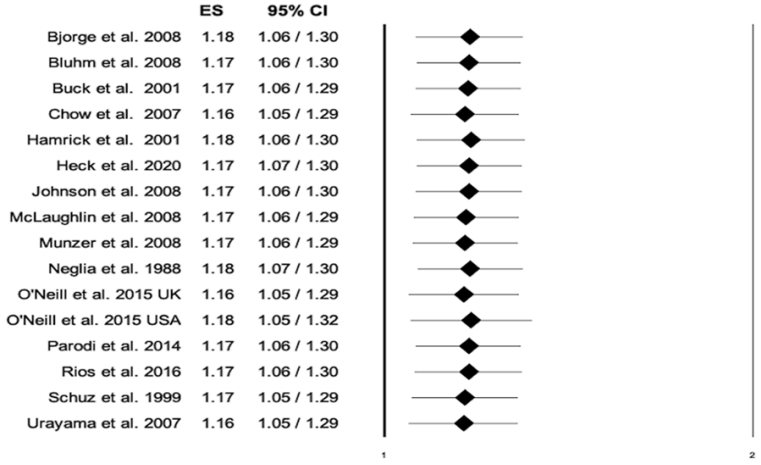

Figure 3. Sensivity analysis for neuroblastoma in participants with high birth weight (>4000).

ticipants, are presented in **Figure 2**. High birth weight was associated with an increased risk of neuroblastoma. This impact measure was the same when the random-effects model and the fixed-effects model were used (OR = 1.17; 95% CI: 1.06-1.29, P = 0.002; heterogeneity: Chi^2 = 2.33, df = 15, I^2 = 0%, P>0.05). Sensitivity analyses were performed by extracting each study separately. No significant change was observed among the studies (df = 15, I^2 = 0%, P>0.05) (**Figure 3**). The pooled estimate was quite robust, according to sensitivity analysis (fixed-effects model): excluding individual study values resulted in pooled ORs ranging from 1.17 (95% CI: 1.05-1.29) to 1.18 (95% CI: 1.07-1.30). Visual inspection of the funnel plots (Figure S1), as well as Begg's test (Z value: -1.14; P = 0.255) and Egger's linear regression test revealed no evidence of publication bias (Intercept: -0.14; P = 0.609).

Low birth weight and neuroblastoma risk

15 studies [10-13, 21-26, 28-31, 35] provided data for the computation of the OR (95% CI) of risk of neuroblastoma in patients with low birth weight (<2500 g) compared to those with birth weights more than this threshold value. **Figure 4** depicts a forest plot with ORs and 95% CIs, as well as the pooled estimate of the risk of neuroblastoma following low birth weight. Low birth weight was associated with an elevated risk of neuroblastoma in both the random-effects model (OR = 1.19; 95% CI: 1.03-1.37, P = 0.017) and the fixed-effects model (OR = 1.19; 95% CI: 1.05-1.36, P = 0.007; heterogeneity: Chi^2 = 16.93, df = 15, I^2 = 0%, P = 0.323). Sensitivity analyses were also performed by extracting each study separately for low birth weight (df = 15, I^2 = 11.42%, P>0.05). No noticeable change was observed in the analysis results. Thus, the robustness of the analysis results was confirmed by sensitivity analysis (**Figure 5**). No noticeable publication bias was observed among the included studies according to the symmetry of the funnel plot (Figure S2), Begg's test (Z-value: -1.93; P = 0.054), and Egger's linear regression test (Intercept: -0.71; P = 0.341).

Subgroup analysis

Subgroup analysis was used to further analyze the connection with both high and low birth weight (as region). In terms of the connection

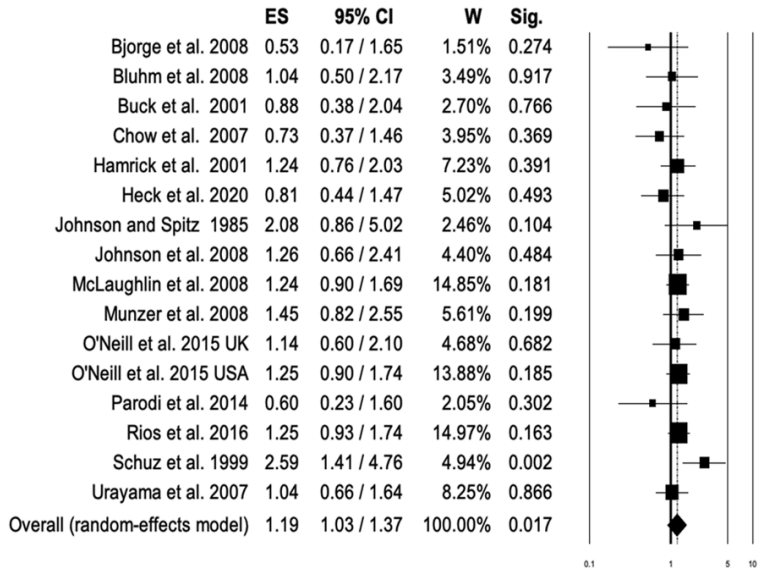

Figure 4. ORs for neuroblastoma in participants with low birth weight (<2500).

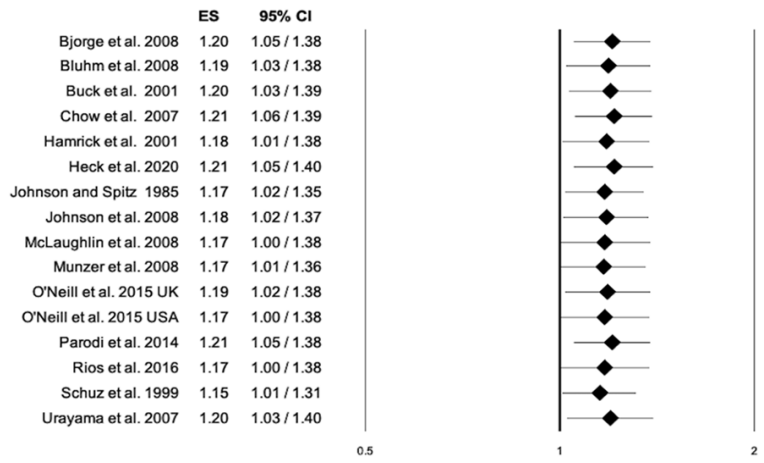

Figure 5. Sensivity analysis for neuroblastoma in participants with low birth weight (<2500).

with high birth weight, region-specific pooled estimates revealed no significant differences (**Table 3**). The relationship with low birth weight and neuroblastoma was stronger in European research than in those conducted in the United States or Canada. The technique used to collect birth weight data had no effect on the strength of the link with high birth weight. In contrast, it had a significant impact on the link with low birth weight: studies that employed interview-based data revealed a >45% higher risk, but those that relied on registry data had a significantly lower estimate. As seen in **Table 3**, although the manner of acquiring the case diagnosis had no significant effect on either the high or low birth weight estimates, the low birth weight estimate was greatly influenced by the source of controls, with registry-based studies having lesser effects.

Discussion

Several prior reports have shown that birth weight is significantly associated with different types of cancer in infants and children [34, 35]. However, it is a well-known fact that there is insufficient evidence in studies on neuroblastoma. A total of 16 papers were included in this systematic review and meta-analysis. 4,361,141 participants worldwide were systematically analyzed, and a meta-analysis was conducted. Individuals with both high and low birth weights may face an increased risk of developing neuroblastoma later in life (OR = 1.17; 95% CI: 1.06-1.29, P = 0.002; OR = 1.19; 95% CI: 1.03-1.37, P = 0.017, respectively). In addition to all these, our sensitivity analyses showed that there may be a bias in relation to low birth weight. Studies using interview method as data source had stronger relationships than studies using recordings. Importantly, the results of our meta-analysis differ in some respects from the results reached by the authors of the individual studies. Namely, Urayama et al. clearly concluded that high birth weight is a risk factor for neuroblastoma [13]. In the studies conducted by Schuz et al. [21], Hemrick et al. [28], and Johnson and Spitz [23], it was concluded that low birth weight was strongly associated with neuroblastoma risk. Similar to our study, four studies [11, 12, 22, 31] reported a U-shaped relationship between birth weight and neuroblastoma. Five study reports [24, 25, 27, 29,

Table 3. The association between birth weight and the neuroblastoma risk: moderator analysis

Characteristics of study	Category	High birth weight OR (95% CI)	Low birth weight OR (95% CI)
Geographic area	North America	1.16 (1.03-1.32)	1.18 (1.00-1.40
	Europe	1.19 (1.01-1.41	1.27 (1.03-1.57)
Source of data for birth weight	Registry	1.17 (1.05-1.31)	1.17 (1.01-1.35)
	Interview	1.21 (1.00-1.45)	1.45 (1.07-1.96)
Source of case diagnosis	Registry	1.20 (1.07-1.34)	1.20 (1.03-1.42)
	Other[a]	1.09 (0.88-1.35)	1.24 (0.99-1.56)
Source of controls	Registry/certificate	1.18 (1.05-1.32)	1.14 (0.97-1.35)
	Other[b]	1.17 (0.97-1.41)	1.36 (1.09-1.69)

[a]Included: death certificates, records, surveillance. [b]Included: population, random digit dialing.

33] stated that there was no significant association between birth weight and neuroblastoma, while the authors of one study did not comment on this issue [10]. It is thought that the authors of the related studies may have overlooked an association with high birth weight, either because it was not statistically significant or because it may have been "masked" because of the selection of the reference layer for birth weight. Very importantly, the birth weight measurement error must be considered at this point. In addition, studies on the relationships between birth weight and disease risks can be confusing in many ways. Correction and sensitivity analyses for confounders were done by matching in the included studies, but the adjusted estimates did not differ significantly from the unadjusted results.

When the relationship between high birth weight and neuroblastoma was examined, there was a significant level of homogeneity between the study results (according to I^2 statistics which a method for assessing study heterogeneity [18]). In addition, sensitivity analyses, a method that excludes each study separately, were performed. There was no noticeable difference in the analysis results. These findings showed that the study was stable and very robust. In addition, studies reporting >4500 (extremely high birth weight) birth weights have reported an increased risk of neuroblastoma [11, 25, 28]. In our subgroup and sensitivity analyses, the relationship between low birth weight and neuroblastoma was also evaluated. A stronger association was reported in the analyses in interview-based studies than in objective sources such as birth records/registry. This suggested that mothers may remember their children born with low birth weight lower than they actually are. To be clear, it is anticipated that there may be a bias in interview-based studies.

It may not be correct to assume that birth weight or fetal growth alone is a causal factor leading to disease risks [36]. At this point, it is important to focus on the main causes and mechanisms that cause the increase or decrease in birth weight. It is a well-known fact that the incidence of several diseases risk continues to increase rapidly worldwide, with lifestyle changes, genetic factors, ethnicity, and environmental factors such as poor nutrition, polluted air, obesity, and sedentary lifestyle. For example, maternal diabetes mellitus, which is one of the factors that stimulate prenatal weight gain, may be a remarkable factor in this respect. It has been clearly shown in some studies that it leads to an increase in birth weight [37, 38]. Similarly, the fact that the mother is overweight during pregnancy can also cause this. However, in terms of neuroblastoma, not only these factors, but also all factors should be considered.

As a result, both high and low birth weight in individuals may be among the important risk factors for neuroblastoma development. At this point, there is an increasing need to investigate, particularly in randomized controlled trials, several other causative factors that may lead to the development of neuroblastoma and high or low birth weight in infants.

Disclosure of conflict of interest

None.

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Table S1. Search strategy

Database	Keywords
PUBMED	
#1	(("births"[All Fields] OR "birthed"[All Fields] OR "birthing"[All Fields] OR "parturition"[MeSH Terms] OR "parturition"[All Fields] OR "birth"[All Fields] OR "births"[All Fields]) AND ("characteristic"[All Fields] OR "characteristics"[All Fields])) OR ("birth weight"[MeSH Terms] OR ("birth"[All Fields] AND "weight"[All Fields]) OR "birth weight"[All Fields]) birth: "birth's"[All Fields] OR "birthed"[All Fields] OR "birthing"[All Fields] OR "parturition"[MeSH Terms] OR "parturition"[All Fields] OR "birth"[All Fields] OR "births"[All Fields] characteristics: "characteristic"[All Fields] OR "characteristics"[All Fields] birth weight: "birth weight"[MeSH Terms] OR ("birth"[All Fields] AND "weight"[All Fields]) OR "birth weight"[All Fields]
#2	"prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatals"[All Fields] OR "perinatal"[All Fields] OR "perinatally"[All Fields] OR "perinatals"[All Fields]
#3	#1 OR #2
#4	"neuroblastoma"[MeSH Terms] OR "neuroblastoma"[All Fields] OR "neuroblastomas"[All Fields]
#5	#3 AND #4
#6	"cross sectional studies"[MeSH Terms] OR ("cross sectional"[All Fields] AND "studies"[All Fields]) OR "cross sectional studies"[All Fields] OR ("cross"[All Fields] AND "sectional"[All Fields] AND "study"[All Fields]) OR "cross sectional study"[All Fields] OR "case-series"[All Fields] OR ("case control studies"[MeSH Terms] OR ("case control"[All Fields] AND "studies"[All Fields]) OR "case control studies"[All Fields] OR ("case"[All Fields] AND "control"[All Fields] AND "study"[All Fields]) OR "case control study"[All Fields]) OR ("follow up studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "follow up studies"[All Fields] OR ("follow"[All Fields] AND "up"[All Fields] AND "study"[All Fields]) OR "follow up study"[All Fields]) OR ("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR ("cohort"[All Fields] AND "study"[All Fields]) OR "cohort study"[All Fields])
#7	#5 AND #6
EMBASE	
S1	((birth or "childbirth" or "delivering the baby" or "giving birth" or "labor delivery" or "parturition" or "parturitions") characteristics) OR ((birth or "childbirth" or "delivering the baby" or "giving birth" or "labor delivery" or "parturition" or "parturitions") weight)
S2	((prenatal or "antenatal")) OR perinatal
S3	S1 OR S2
S4	neuroblastoma
S5	S3 AND S4
S6	(((((((cross-sectional study) or "synchronic study")) or ("synchronic study" or "cross-sectional study"))) or (("synchronic study" or "cross-sectional study") or ("cross-sectional study" or "synchronic study")))) OR case-series OR (case-control study) OR (((((((cohort study) or "follow-up study")) or ("follow-up study" or "cohort study"))) or (("follow-up study" or "cohort study") or ("cohort study" or "follow-up study"))))
S7	S5 AND S6
WoS	
#1	(ALL=(birth characteristics)) OR ALL=(birth weight)
#2	(ALL=(prenatal)) OR ALL=(perinatal)
#3	ALL=(neuroblastoma)
#4	(#1) OR #2
#5	(#3) AND #4
#6	((((((ALL=(cross-sectional study)) OR ALL=(synchronic study)) OR ALL=(case-series)) OR ALL=(case-control study)) OR ALL=(follow-up study)) OR ALL=(cohort study)
#7	(#6) AND #5

SCOPUS	
#1	birth AND characteristics OR birth AND weight
#2	prenatal OR perinatal
#3	#2 OR #1
#4	neuroblastoma
#5	#3 AND #4
#6	cross-sectional AND study OR synchronic AND study OR case-series OR case-control AND study OR follow-up AND study OR cohort AND study
#7	#6 AND #5

Table S2. Methodological quality assessment of studies included in meta analysis

Nr.	First author	Design	Selection	Comparability	Outcome/Exposure	Total
1	Bjorge (2008) [25]	Cohort	***	**	**	*******
2	Bluhm (2008) [26]	Case-control	***	**	**	*******
3	Buck (2001) [10]	Case-control	**	***	**	*******
4	Chow (2007) [27]	Case-control	***	**	***	********
5	Hamrick (2001) [28]	Case-control	***	***	**	********
6	Johnson and Spitz (1985) [23]	Case-control	**	**	**	******
7	Johnson (2008) [29]	Case-control	***	**	***	********
8	McLaughlin (2008) [11]	Case-control	***	***	**	********
9	Munzer (2008) [12]	Case-control	***	***	**	********
10	Neglia (1988) [24]	Case-control	***	***	**	********
11	O'Neill (2015) [22]	Case-control	***	**	**	*******
12	O'Neill (2015) [22]	Case-control	**	**	***	*******
13	Parodi (2014) [30]	Case-control	**	**	**	******
14	Rios (2016) [31]	Case-control	***	***	**	********
15	Schuz (1999) [32]	Case-control	***	***	**	********
16	Uruyama (2007) [13]	Case-control	***	***	**	********
17	Heck (2020) [33]	Cohort	**	***	**	*******

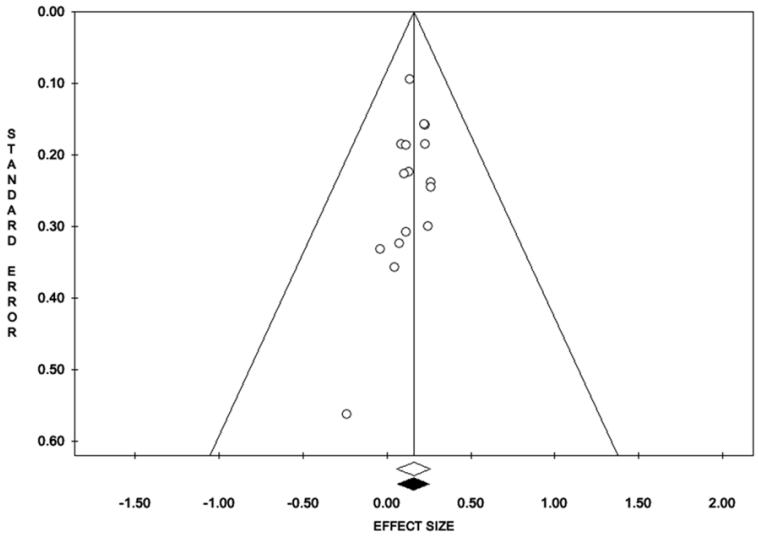

Figure S1. Funnel plot showing the high birth weight and neuroblastoma risk.

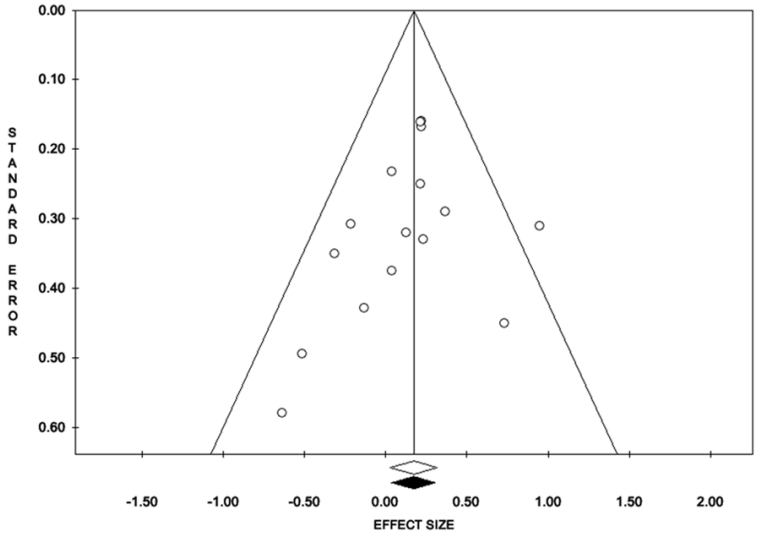

Figure S2. Funnel plot showing the low birth weight and neuroblastoma risk.