



Birth Weight and Subsequent Risk of Total Leukemia and Acute Leukemia: A Systematic Review and Meta-Analysis

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Objective: Birth weight, an important indicator of fetal nutrition and degree of development, may affect the risk of subsequent leukemia. At present, little is known about the effect of birth weight on acute myeloid leukemia (AML) and whether there is a dose-dependent relationship of birth weight with acute lymphoid leukemia (ALL) and AML. To address these questions, the present work aimed to systematically investigate the relationship between birth weight and the risk of subsequent leukemia based on the current epidemiological studies

Methods: Relevant studies were systematically retrieved from electronic databases PubMed, Embase, and Cochrane Library, from inception to May 15th, 2021. Finally, 28 studies (including 21 case-control studies and 7 cohort studies) were included for the final meta-analysis. Results in cohort studies were performed by risk ratios (RRs), while those in case-control studies by odds ratios (ORs), and all results were assessed by adopting the random-effect model. Besides, a dose-dependent analysis was conducted based on the cohort studies.

Results: Compared with the population with normal birth weight (NBW), the population with high birth weight (HBW) might have an increased risk of leukemia (OR 1.33, 95%CI 1.20–1.49; I^2 0%). Meanwhile, low birth weight (LBW) was associated with a decreased risk of ALL, as evidenced from the pooled analysis of case-control studies (OR 0.83, 95% CI 0.75–0.92; I^2 23.3%). However, relative to NBW population, the HBW population might have an increased risk of ALL (OR 1.28, 95% CI 1.20–1.35; I^2 7%). There was no obvious evidence supporting the relationship between LBW and the risk of AML from the pooled analysis of case-control studies (OR, 1.11 95% CI 0.87–1.42; I^2 31.7%).

Conclusions: Overall, in children and young adults, HBW population may be associated with the risks of subsequent leukemia and AML relative to NBW population, but the supporting dose-dependent evidence is lacking. In addition, compared with NBW

population, there is stronger evidence supporting a significantly increased risk of subsequent ALL in HBW population, and a decreased risk in LBW population in a dose-dependent manner. More prospective studies with large samples are warranted in the future to validate and complement these findings.

Keywords: leukemia, acute leukemia, meta-analysis, high birth weight, low birth weight

INTRODUCTION

Leukemia is a malignant clonal disease of hematopoietic stem cells (HSCs). It is characterized by the uncontrolled proliferation and development of leukocytes in the bone marrow and peripheral blood, which in turn invade the internal organs, such as the liver and spleen (1–3). Leukemia, a common hematologic tumor, remains the most common cancer in children. In general, leukemia can be classified into acute and chronic subtypes according to the disease progression degree, of them, acute leukemia is the most common in clinical work. Acute leukemia encompasses acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML). Typically, ALL has been reported to account for approximately 80% of all the diagnosed leukemia cases in children aged 0–19 years, while AML accounts for 15–20% (4). Some perinatal features (such as gestational age, gender, and birth order) and maternal features (like age) are associated with the risk of childhood leukemia. However, the associations of other features with leukemia, especially with the leukemia subtypes, remain to be further elucidated. Currently, the pathogenesis of leukemia is unclear. Typically, exposure early in life may lead to dramatic health consequences, including the risk of cancer in the childhood and throughout the life of an individual (5).

Birth weight, an important indicator of fetal nutrition and degree of development, may affect the risk of subsequent leukemia. Although several previous studies have suggested that high birth weight (HBW) increases the risk of subsequent ALL, the results are inconsistent (6–9). Nevertheless, little is known about the effect of birth weight on AML and whether there is a dose-dependent relationship between birth weight and ALL/AML. To address these questions, this study aimed to systematically investigate the relationship between birth weight and the risk of subsequent leukemia based on existing epidemiological studies.

METHODS

This meta-analysis was conducted according to the guidance of Meta-analyses of Observational Studies in Epidemiology (MOOSE) (10). Two investigators (Che and Long) systematically searched the electronic databases PubMed, Embase, and Cochrane Library, from inception to May 15th, 2021, without language restriction. Two groups of medical subject terms (MeSH), including “birth weight” and “leukemia,” were used for study search. Meanwhile, Boolean operator “OR” was used within groups, whereas “AND” was used between groups. To identify more relevant studies, the library entries were retrieved manually. Besides, previous meta-analyses were also reviewed if

applicable. The detailed search flow is displayed in Appendix 1 (**Supplementary Material**).

Study Selection

Inclusion criteria were determined following the PICOS standards: (1) The study population did not have any family history of cancers, exposure to radiation and chemicals, or congenital disease (such as Down’s syndrome), with birth weight being the interested exposure. (2) Different birth weight levels were compared. (3) One birth weight group served as the control or reference group. (4) The study outcomes reported the incidence of leukemia. (5) The study types were restricted to case-controlled, cohort studies, or randomized controlled trials (RCTs). (6) The related odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were available or might be calculated. Meanwhile, the exclusion criteria were as follows: (1) The study population had a family history of cancers, exposure to radiation and chemicals, or congenital disease like Down’s syndrome, and birth weight was not the interested exposure. (2) The studies did not report the risk of leukemia or acute leukemia by comparing different birth weight levels. (3) Cross-sectional studies, pooled studies, case reports or series, conference abstracts should be excluded. (4) Related ORs, RRs, or HRs were not obtained or converted.

Data Extraction and Quality Assessment

An unified list was used to extract the following baseline data from the included studies, including first author, publication year, country, sample size, date of birth or diagnosis, BMI categories, types of leukemia, ascertainment of leukemia, and maximum adjusted variables. The maximum variables adjusted for ORs, RRs, or HRs were extracted. Any disagreements were solved by the opinion from a third investigator. The quality of included studies was evaluated by using the Newcastle-Ottawa Scale (NOS) items, with the total score of 9 stars (11). Studies with a score ≥ 6 stars were considered as high-quality studies, otherwise, they were the low-quality studies.

Statistical Analysis

Referring to most of the included studies, this study defined birth weight $\leq 2,500$ g, 2,500–4,000 g, $\geq 4,000$ g as “low birth weight (LBW),” “normal birth weight (NBW),” and “HBW,” respectively. When one study reported different LBWs or HBWs (such as $\leq 2,000$ g, 2,000–2,500, 4,000–4,500 g, $\geq 4,500$ g), it was analyzed separately. The primary endpoint of our study was to qualitatively analyze the relationship between birth weight and leukemia/acute leukemia (like LBW vs. NBW, HBW vs.

NBW). Generally speaking, HRs can be roughly considered to be equal to RRs in cohort studies (12). Therefore, results of all the cohort studies were performed by RRs, whereas those of case-control studies by ORs. Statistical heterogeneity was evaluated using I^2 statistics, with the I^2 values of 25, 50, and 75% indicating low, moderate, and high inconsistency, respectively (13). If there were high heterogeneities between studies, subgroup and sensitivity analyses were performed to explore the possible sources of heterogeneity between groups, and meta-regression analysis was further carried out in the case of enough included studies ($n > 10$). This study used a random-effects model to more conservatively estimate the pooled RRs and ORs, since more robust results were obtained after aggregating with this model. In addition, the risk of potential publication bias was assessed by funnel plots as well as Begg's and Egger's tests (14, 15). Trim and fill analyses were performed if necessary.

The secondary endpoint of this study was to quantitatively assess the effect of birth weight on leukemia. For this purpose, a dose-response meta-analysis was performed on the included cohort studies. To maximally include the available cohort studies, the robust error meta-regression method described by Xu and Doi (16) was utilized to establish a potential dose-response relationship between birth weight and leukemia. In this "one-stage" framework approach, each of the included studies was considered as a cluster across the whole population, so long as the study included at least two categories.

In this paper, the restricted cubic spline was utilized to fit the potential non-linear trend with 3 knots, and non-linear p -values were calculated by testing the second spline coefficients to zero. The non-linear model was adopted when the non-linear $p < 0.05$; otherwise, the linear model was used. In general, the lowest-dose category should be used as a reference in the included studies; however, when the non-lowest-dose studies were used as reference, they were converted via an Excel macro file produced by Hamling et al. (17) based on the Greenland and Longnecker's (18) theory. The corresponding authors were contacted when the number of cases in a particular category was missing. Also, when the open intervals were studied, the amplitude was assumed to be the same as the adjacent category or 1.2-fold of the node (19). All statistical analyses were performed by Stata 12.0E.

RESULTS

At first, a total of 4,024 studies were included. After removing 566 duplicated studies, 3,458 studies were retained. Then, the titles and abstracts of these 3,458 studies were read, and 3,370 unrelated studies were further excluded; as a result, only 88 studies were left for full-text review. Finally, only 28 studies (including 21 case-control and 7 cohort studies) were included, as shown in **Figure 1**. The specific reasons of exclusion were listed as follows: (1) reviews ($n = 12$); (2) no available information of birth weight ($n = 16$); (3) the study endpoints did not include the risk of leukemia ($n = 8$); (4) pooled studies, letters ($n = 8$); and (5) case reports, conference abstracts ($n = 16$).

In the 28 studies, participants were children and young adults <29 years of age. Among the 21 case-control studies (6–9, 20–36), 21 involving altogether 111,643 participants (both cases and controls) reported the association between birth weight and the risk of ALL; 14 including 82,566 participants (both cases and controls) mentioned the relationship between birth weight and the risk of AML; while 7 containing 43,501 participants (both cases and controls) reported the association between birth weight and the risk of total leukemia. Among the 7 cohort studies (37–43), 5 recruiting altogether 4,807,631 participants mentioned the relationship between birth weight and the risk of ALL; 3 including 4,143,450 participants reported the association between birth weight and the risk of AML; and 4 containing 2,261,005 participants stated the relationship between birth weight and the risk of total leukemia. More details about the baseline characteristics are displayed in **Table 1**. In addition, all the included studies had a score ≥ 6 stars and were considered as high-quality studies, as shown in **Supplementary Table 1**.

Meta-Analysis

Total Leukemia

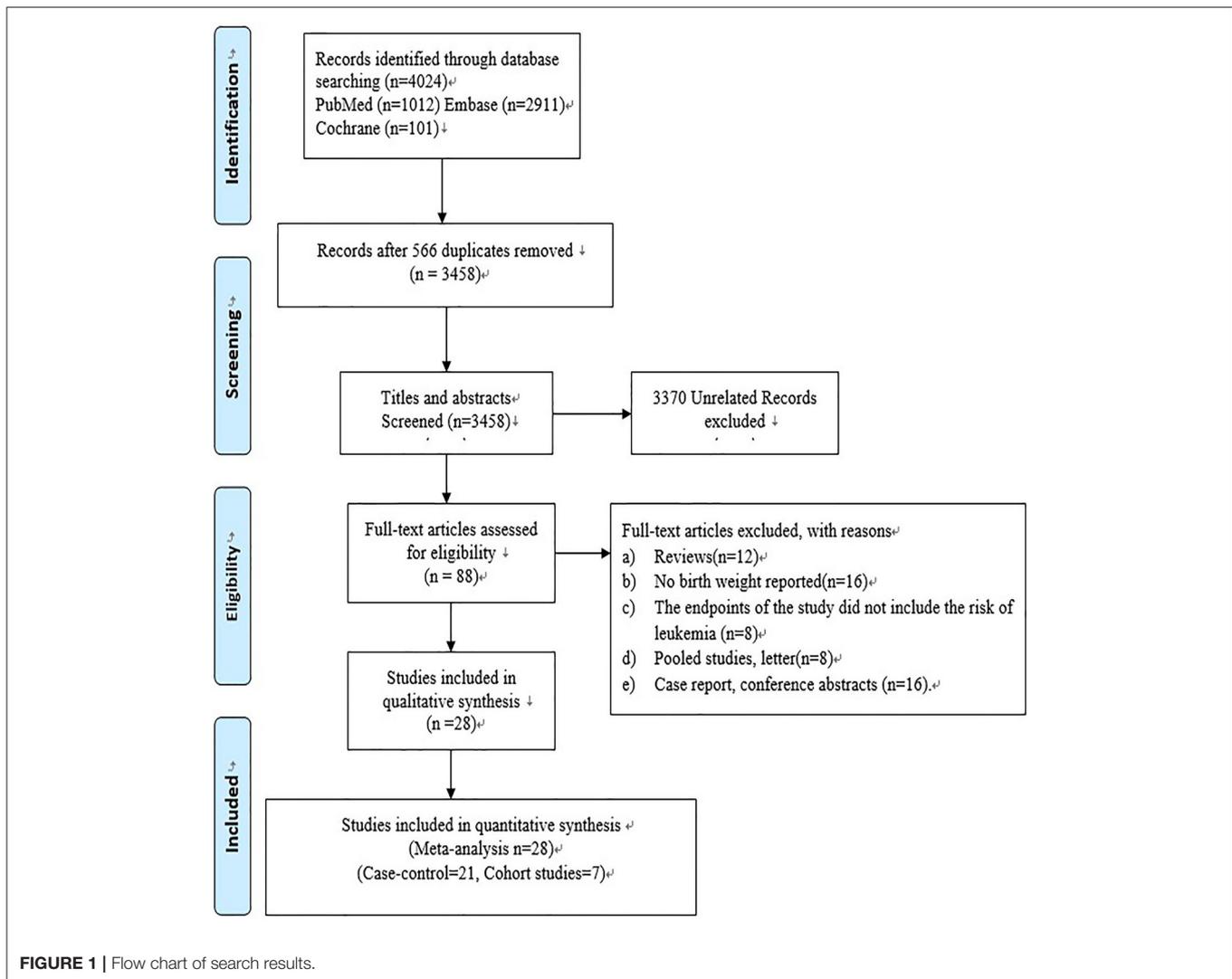
As presented in **Figure 2**, no obvious evidence was found between LBW and the risk of total leukemia from the pooled analysis of enrolled case-control studies (OR 0.90, 95% CI 0.75–1.07; I^2 27.6%). Compared with the NBW population, the HBW population might have an increased risk of leukemia (OR 1.33, 95% CI 1.20–1.49; I^2 0%). The potential publication bias was evaluated by the funnel plot, as shown in **Supplementary Figure 1A**. Visually, the funnel plot was symmetrical, and both Begg's ($p = 1.00$) and Egger's ($p = 0.881$) tests did not reveal any evidence of publication bias. Moreover, sensitivity analysis was conducted by removing one study each time, and the pooled results showed little change, as shown in **Supplementary Figure 2**.

Compared with the NBW population, no obvious evidence was detected between LBW/HBW and the risk of leukemia from the pooled analysis of 4 cohort studies (RR 0.94, 95% CI 0.68–1.30; I^2 0% for LBW; RR 1.27, 95% CI 0.89–1.83; I^2 31% for HBW), respectively, as presented in **Supplementary Figure 3A**. Due to the limited number of available studies, publication bias test and sensitivity analysis were not conducted further.

According to **Supplementary Figure 4A**, the dose-response analysis from 4 cohort studies showed that the risk of leukemia did not increase with the increase in birth weight.

ALL

It was demonstrated from **Figure 3** that, there was obvious evidence supporting that LBW was related to a decreased risk of ALL from the pooled analysis of case-control studies (OR 0.83, 95%CI 0.75–0.92; I^2 23.3%). However, compared with the NBW population, the HBW population might have an increased risk of ALL (OR 1.28, 95%CI 1.20–1.35; I^2 7%). In addition, the publication bias was evaluated by the funnel plot, as presented in **Supplementary Figure 1B**. Visually, the funnel plot was asymmetrical, and both Begg's ($p = 0.203$) and Egger's ($p = 0.256$) tests revealed no obvious evidence of publication bias. Also, sensitivity analysis was conducted by removing one study



each time, and the pooled results showed slight change, as shown in **Supplementary Figure 5**.

Similar results were obtained the pooled analysis of cohort studies, suggesting that the LBW population had a decreased risk of ALL compared with the NBW population (RR 0.66, 95% CI 0.47–0.93; I^2 0%), and the HBW population had an increased risk of ALL (RR 1.49, 95% CI 1.16–1.91; I^2 0%), as observed from **Supplementary Figure 3B**. Due to the limited number of available studies, the publication bias test and sensitivity analysis were not conducted further.

As observed from **Supplementary Figure 4B**, the dose-response analysis of 5 cohort studies showed that the risk of ALL significantly increased when the birth weight increased from 1,750 to 5,000 g.

AML

In **Figure 4**, there was no obvious evidence supporting the relationship between LBW and the risk of AML, as evidenced from the pooled analysis of case-control studies (OR, 1.11 95%

CI 0.87–1.42; I^2 31.7%). Similarly, compared with the NBW population, the HBW population was not associated with an increased risk of AML (OR 1.23, 95% CI 0.97–1.56; I^2 36.7%). Besides, the publication bias was assessed by the funnel plot, as displayed in **Supplementary Figure 1C**. Visually, the funnel plot was asymmetrical, meanwhile, Begger's ($p = 0.650$) and Egger's ($p = 0.434$) tests did not indicate any evidence of publication bias. Also, sensitivity analysis was conducted by removing one study each time, and the pooled results showed little change, as shown in **Supplementary Figure 6**.

Results from the pooled analysis of cohort studies demonstrated that the HBW population had an increased risk of AML compared with the NBW population (RR 1.88, 95% CI 1.10–3.22; I^2 0%), as observed from **Supplementary Figure 1**. Due to the limited number of available studies, the publication test and sensitivity analysis were not conducted further.

However, the dose-response analysis of 3 cohort studies suggested that the risk of AML did not significantly

TABLE 1 | The detailed baseline information of 28 observational studies.

Author, year	Country	Sample size	Birth or diagnosed period	Birth weight categories (g)	Types of leukemia	Ascertainment of leukemia	Maximum adjusted variables
Cohort studies							
Stacy et al. (37)	USA	1,877,078	2003–2015	<2,000; 2,000–2,499; 3,000–3,499; 3,500–3,999; 4,000–4,499; \geq 4,500	Total	International classification of childhood cancer	Maternal age, race, sex at birth, gestational age
Paltiel et al. (38)	Israel	88,829	1964–1976	\leq 2,999; 3,000–3,499; 3,500–3,999; \geq 4,000	Total, ALL, AML	ICD-9	Maternal origin, mother age, father age, gender, socioeconomic status
Heck et al. (39)	China	2,079,037	2004–2014	<2,500 g; 2,500–3,999 g; \geq 4,000	ALL, AML	ICD-9 ICD-O-3	Mother's age, father's age, family income, urbanization level of residence at birth
Lee et al. (40)	Singapore	229,248	1992–1999	2,500–3,500; >3,500	Total, ALL	ICCC	Gender, gestational age, birth order, maternal age
Murray et al. (41)	UK	434,933	1971–1986	<3,500 g; \geq 3,500	ALL	Medical records	Maternal age, birth order, Down's syndrome, gestational age, gender, social class
Spracklen et al. (42)	USA	65,850	1993–1998	<2,721; 2,721–3,624; 3,624–4,490; \geq 4,490	Total	Medical records	Age, race, education, normalized socioeconomic status, BMI, smoking status, alcohol use
Westergaard et al. (43)	Denmark	1,975,584	1968–1992	<2,510; 2,510–3,009; 3,010–3,509; 3,510–4,009; 4,010–4,509; \geq 4,510	ALL, AML	ICO	Gender, gestational age, maternal age, birth order calendar period
Case-control							
Jiménez-Hernández et al. (20)	Mexico	Case 1,455 Control 1,455	2010–2015	<2,500; 2,500–3,499; 3,500–4,000; >4,000	ALL, AML	Medical Records	Child's sex, overcrowding index, birth order, mother's age at the time of pregnancy
Barahmani et al. (24)	USA	Case 575 Control 11,379	1995–2003	\leq 2,500; 2,500–3,999; \geq 4,000	ALL	Medical records	Infant gender, maternal age
Dorak et al. (28)	UK	Case 732 Control 3,723	1968–1992	\leq 2,500; 2,500–2,999; 3,000–3,499; 3,500–3,999; \geq 4,000	ALL	Medical records	None
Hjalgrim et al. (29)	Denmark	Case 2,204 Control 10,745	1984–1999	<1,500; 1,500–1,999; 2,000–2,499; 2,500–2,999; 3,000–3,499; 3,500–3,999; 4,000–4,499; \geq 4,500	ALL, AML	FAB classification M0–M7	None
Koifman et al. (6)	Brazil	Case 201 Control 440	1999–2005	<2,500; 2,500–2,999; 3,000–3,499; 3,500–3,999; \geq 4,000	Total, ALL, AML	Medical records	Gender, income, maternal age, hormone intake, pesticide exposure during pregnancy
Groves et al. (25)	USA	Case 401 Control 1,592	1995–2002	\leq 2,500; 2,500–3,999; \geq 4,000	ALL	Medical records	None

(Continued)

TABLE 1 | Continued

Author, year	Country	Sample size	Birth or diagnosed period	Birth weight categories (g)	Types of leukemia	Ascertainment of leukemia	Maximum adjusted variables
Ma et al. (7)	USA	Case 366 Control 460	1995–2002	≤2,500; 2,500–3,999; ≥4,000	ALL, AML	Medical records	Household income, maternal education
Oksuzyan et al. (9)	USA	Case 5,788 Control 5,788	1988–2008	<2,500; 2,500–3,000; 3,000–3,500; 3,500–4,000; 4,000–4,500; ≥4,500	Total, ALL, AML	Medical records	Gestational age, birth order, mother's age, father's education, child's race, and payment source for delivery
Ou et al. (30)	USA	Case 1,842 Control 1,986	1989–1993	≤3,000; 3,001–3,500; 3,501–4,000; >4,000	ALL	Medical records	Socioeconomic status, maternal age, race
Podvin et al. (31)	USA	Case 595 Control 5,950	1981–2002	≤2,500; 2,500–3,999; ≥4,000	Total, ALL, AML	ICD-O-3	Maternal age
Reynolds et al. (32)	USA	Case 1,728 Control 2,802	1988–1997	≤2,500; 2,500–3,999; ≥4,000	ALL, AML	Medical records	Gestational age
Smith et al. (34)	UK	Case 3,651 Control 6,337	1991–1996	≤2,500; 2,500–3,999; ≥4,000	Total, ALL, AML	Medical records	study region, sex and age
Sprehe et al. (35)	USA	Case 2,254 Control 11,734	1995–2003	≤2,500; 2,500–3,999; ≥4,000	Total, ALL, AML	Medical records	Birth year, gestational age, maternal age
Yeazel et al. (36)	USA	Case 3,711 Control 816	1982–1989	≤2,797; 2,798–3,291; 3,292–3,547; 3,548–3,859; >3,859	ALL, AML	Medical records	Maternal age, birth order, gestational age, gender
Roman et al. (26)	UK	Case 128 Control 286	1962–1992	<2,500; 2,500–3,500; >3,500	Total, ALL, AML	Medical records	Gender, age, study region
Schüz et al. (21)	Germ total	Case 755 Control 2,057	1992–1994	≤2,500; 2,500–3,999; ≥4,000	ALL, AML	Medical records	Maternal age, degree of urbanization, and socioeconomic status
McLaughlin et al. (23)	USA	Case 148 Control 9,667	1985–2001	<2,500; 2,500–2,999; 3,000–3,499; 3,500–3,999; 4,000–4,499; ≥4,500	ALL, AML	ICD-O-3	Birth year, gender, race, and ethnicity, maternal age
Jourdan-Da Silva et al. (22)	USA	Case 473 Control 567	1995–1998	<2,500; 2,500–2,999; 3,000–3,499; 3,500–3,999; ≥4,000	ALL, AML	Medical records	Gender, age at diagnosis, region of residence at diagnosis
Cnatingius et al. (27)	Sweden	Case 610 Control 3,061	1973–1989	<1,500; 1,500–1,999; 2,000–2,499; 2,500–2,999; 3,000–3,499; 3,500–3,999; 4,000–4,499; ≥4,500	ALL	ICD-7	Gestational age
Okcu et al. (8)	USA	Case 104 Control 245	1995	2,500–3,999; ≥4,000	Total, ALL	Medical records	Year of birth, gender, gestational age, maternal age, Oksuzyan tobacco use, parity, race/ethnicity
Savitz et al. (33)	USA	Case 68 Control 208	1976–1983	≤2,500; 2,500–3,999; ≥4,000	ALL	Medical records	None

ICD-9, International Classification of Diseases, Ninth Revision codes; ICD-O-3, International Classification of Diseases for Oncology, Version 3; ICD-7, International Classification of Diseases Seventh Revision; ICO, International Classification of Diseases for Oncology, FAB classification M0–M7, French American, and British classification system; ICC, International Childhood Cancer Classification.

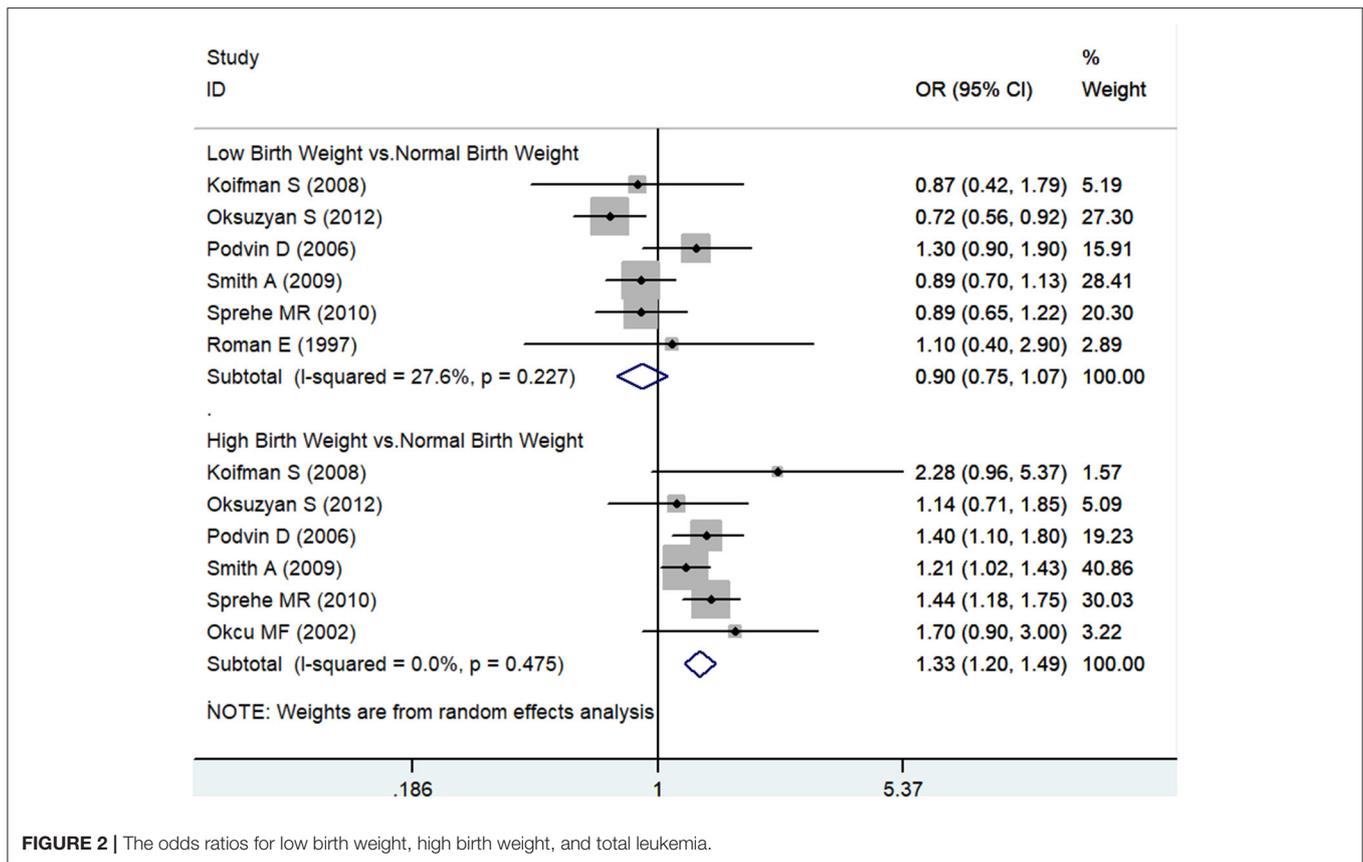


FIGURE 2 | The odds ratios for low birth weight, high birth weight, and total leukemia.

increase with the increase in birth weight, as shown in **Supplementary Figure 4C**.

Subgroup Analysis and Meta-Regression

A moderate heterogeneity was found in the association between birth weight and AML, therefore, subgroup analysis and meta-regression were performed based on the features below, including child age, sample size, publication year, country, and study quality (**Table 2**). According to subgroup analysis, child age and study quality might be the potential sources of heterogeneity between LBW and AML, whereas sample size, child age, publication year, country, and study quality might be the potential sources of heterogeneity between HBW and AML. However, no potential source of heterogeneity was detected through meta-regression.

DISCUSSION

This meta-analysis suggested that LBW might not increase the risk of total leukemia, ALL, or AML compared with NBW. In contrast, the risk of ALL significantly decreased in the LBW population. In the HBW population, HBW might increase the risk of total leukemia and AML, but there was no dose-response relationship. In addition, compared with the NBW population, the HBW population had an increased risk of ALL, and similar

results were obtained from the dose-response analysis of birth weight from 1,750 to 5,000 g.

Birth weight is determined by the nutritional, metabolic, and endocrine differences in the intrauterine environment, and is necessarily closely related to maternal prenatal health and nutritional status. The study by Wiemels et al. showed that chromosomal translocation in acute leukemia, a genetic event, might begin *in utero* (44). In addition, birth weight has been reported to be associated with multiple growth factors in the intrauterine environments, like insulin-like growth factor-1 (IGF-1), sex steroid hormones, and insulin-like growth factor II (IGF-II) (45, 46). *In utero*, growth factors are related to the increased total number of stem cells, which may increase the risks of transformation into tumor cells and leukemia (47). Moreover, IGF-1 is an important embryonic growth factor that increases the stem cell pools in humans and animals. Further, several other hormones and growth factors related to birth weight and stem cell size, including IGF binding protein-3, estriol, and testosterone, can significantly increase the stem cell pool (45).

Birth weight and the risk of subsequent leukemia are often the consequences of multiple reproductive factors including gestational age, race, diet, and micronutrients. As reported in the study by Barahmani et al., the offspring of Hispanic whites with large gestational age were associated with a 50% increased risk of ALL compared to the non-Hispanic whites (24). Besides, a study from Denver indicates that animal

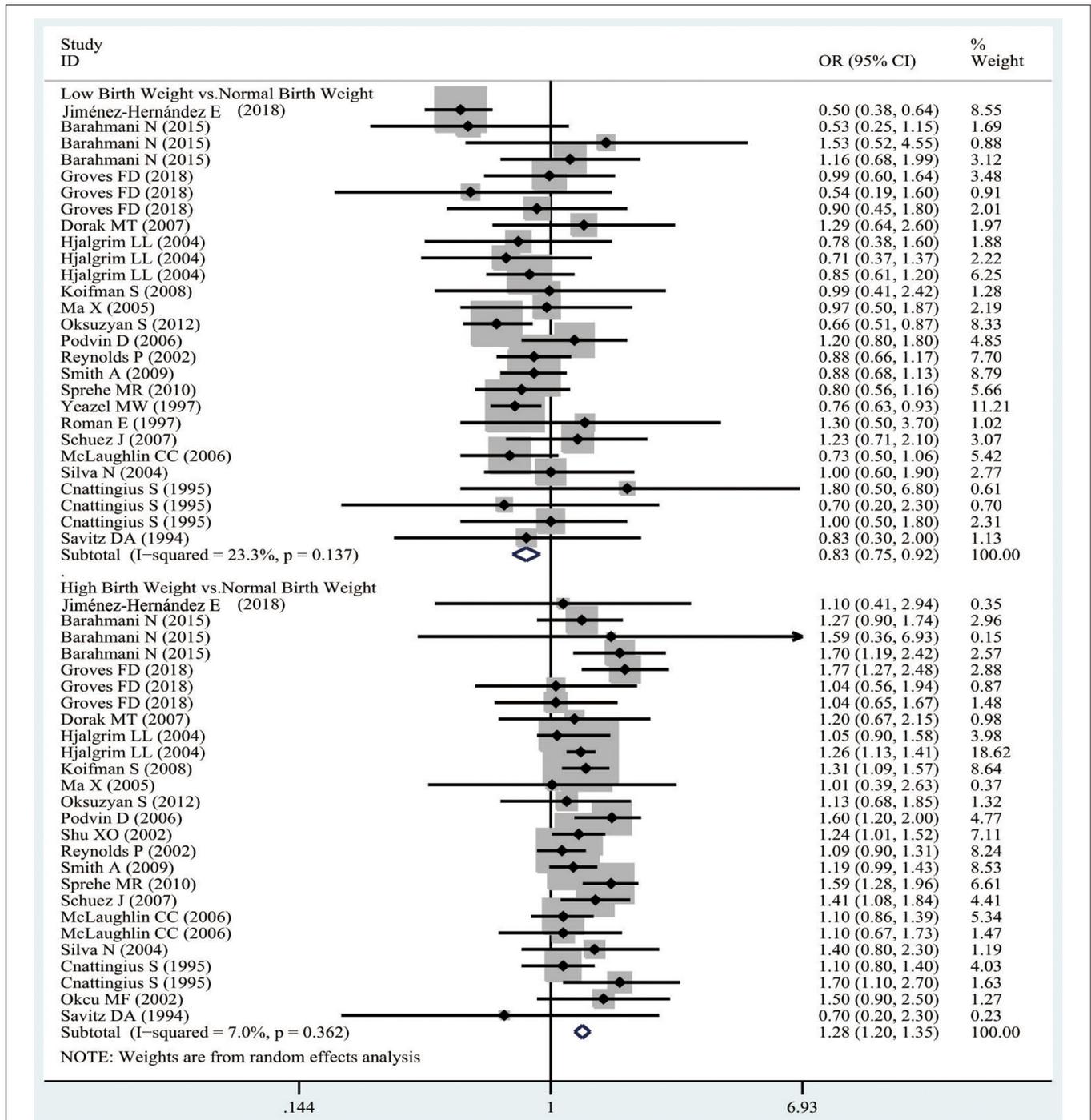


FIGURE 3 | The odds ratios for low birth weight, high birth weight, and ALL.

foods are rich in iron, while plant foods may hinder iron absorption, and the increased iron absorption may increase the risk of ALL in children (48). Meanwhile, another meta-analysis shows that an increased maternal iron intake by 10 mg per day is associated with an increased offspring birth weight by 15.1 g (49).

Although some existing biological evidence suggests that a larger birth size may indicate that more cells are at risk of carcinogenesis (50, 51), the exact mechanism remains unclear. LBW may reflect a poor intrauterine environment or impaired fetal nutrition. In addition, it may also be associated with certain complications during the maternal pregnancy, such as

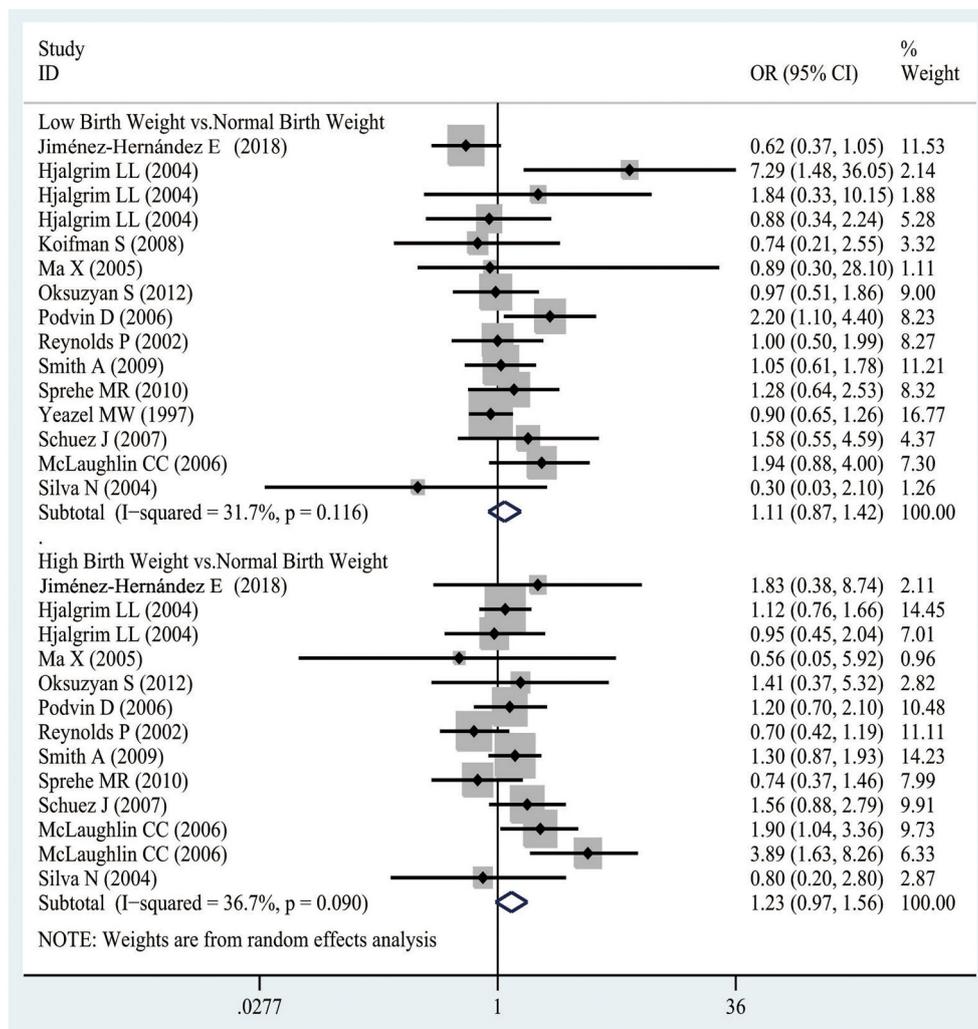


FIGURE 4 | The odds ratios for low birth weight, high birth weight, and AML.

intrauterine growth restriction (IUGR), preeclampsia, or preterm delivery. However, there is still no well-understood mechanism to explain this negative association of LBW with ALL.

Noteworthy, the present study has the following strengths. First, this was the first dose-response analysis that quantitatively assessed the association between birth weight and the risk of leukemia. Meanwhile, all the available studies were included for qualitative analysis, which verified and supplemented the dose-response analysis. Second, there was low inter-heterogeneity between the studies, which enabled the homogeneity between studies. Third, all the extracted ORs or RRs were adjusted by maximum variables, and the random-effect model was adopted to improve the stability of the pooled results.

Inevitably, certain limitations should also be noted in this study. First, most of the included studies were originated from America, Europe, and Asia, while there were relatively few studies from other regions, and the impact on research remained

unclear. Meanwhile, the number of cohort studies was limited, which made it impossible for further analysis. Second, this meta-analysis suggested that HBW was associated with a high risk of leukemia, but whether there is a causal relationship between the two remains to be further investigated. Besides, the impacts of other potential perinatal variables (including full-term or preterm birth, birth order, breastfeeding, or feeding) and maternal characteristics (like the presence of maternal diseases and complications such as diabetes, eclampsia, maternal age, and weight) on our results remained to be further confirmed. Although all of the extracted ORs or RRs were adjusted by the maximum variables, the effects of residual confounding variables were still unknown. Third, the dose-response analyses on birth weight were conducted within the range of 1,750–5,000 g, and the results beyond this range were still unknown. Last but not least, all the populations included in the study were children and young adults (<29 years), and the effect of birth weight on the risk of leukemia beyond this range is still unknown.

TABLE 2 | Subgroup analysis for birth weight and AML.

Items	Low birth weight				High birth weight			
	<i>n</i>	OR, 95% CI; <i>I</i> ²	<i>p</i> ^a	<i>p</i> ^b	<i>n</i>	OR, 95% CI; <i>I</i> ²	<i>p</i> ^a	<i>p</i> ^b
Sample size (cases)				0.414				0.577
≥500	9	1.1 (0.84–1.44); 38.5%	0.093		8	1.1 (0.91–1.33); 0%	0.532	
<500	4	1.12 (0.53–2.37); 20.8%	0.285		3	1.86 (0.93–3.74); 45.9%	0.136	
Children age				0.537				0.632
10+ years	9	1.08 (0.79–1.49); 41.5%	0.072		8	1.22 (0.99–1.50); 0%	0.961	
≤10 years	4	1.25 (0.82–1.85); 0%	0.498		3	1.36 (0.64–2.87); 81.8%	0.001	
Published year				0.996				0.460
≥2010	3	0.87 (0.57–1.34); 31.7%	0.231		3	0.94 (0.53–1.66); 0%	0.469	
<2010	10	1.22 (0.91–1.64); 29.9%	0.153		8	1.28 (0.97–1.67); 45.6%	0.056	
Country				0.642				0.944
America	10	1.04 (0.79–1.38); 33.3%	0.141		8	1.25 (0.82–1.91); 54.4%	0.025	
Europe	3	1.40 (0.8–2.45); 33.4%	0.198		3	1.23 (0.97–1.56); 0%	0.707	
Study quality				0.185				0.272
8–9	8	1.41 (0.97–2.05); 23.8%	0.224		7	1.38 (1.08–1.77); 28.1%	0.195	
6–7	5	0.89 (0.71–1.12); 0%	0.541		4	0.8 (0.54–1.17); 0%	0.559	

p^a for heterogeneity within each subgroup. *p*^b for heterogeneity between subgroups with meta-regression analysis.

CONCLUSIONS

Overall, in children and young adults, HBW may be related to an increased risk of subsequent leukemia and AML in HBW population compared with the NBW population, but support from dose-dependent evidence is lacking. In addition, stronger evidence supports a significantly increased risk of subsequent ALL in the HBW population compared with the NBW population, whereas a decreased risk in the LBW population, and this association is also found in the dose-response. More prospective studies with large samples are still warranted in the future to validate and complement these findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

HC participated in the data collection, data review, relevant data extraction, data analysis, statistical analysis, and the writing of the manuscript. DL, QS, and YL participated in checking data

extraction as well as in the data analysis, statistical analysis, and the writing of the manuscript. LW participated in checking data extraction as well as in the statistical analysis and the writing of the manuscript. All authors saw and approved the final version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fped.2021.722471/full#supplementary-material>

Supplementary Figure 1 | The plots of the funnel for birth weight and Total leukemia (A), ALL (B), and AML (C).

Supplementary Figure 2 | The sensitivity analyses for low birth weight (A), high birth weight (B), and Total leukemia.

Supplementary Figure 3 | The RRs of birth weight and total leukemia (A), AML (B), and ALL (C).

Supplementary Figure 4 | The dose-response of birth weight and total leukemia (A), AML (B), and ALL (C).

Supplementary Figure 5 | The sensitivity analyses for low birth weight (A), high birth weight (B), and ALL.

Supplementary Figure 6 | The sensitivity analyses for low birth weight (A), high birth weight (B), and AML.

Supplementary Table 1 | Quality assessment of the 28 observational studies.

REFERENCES

- Kampen KR. The discovery and early understanding of leukemia. *Leuk. Res.* (2012) 36:6–13. doi: 10.1016/j.leukres.2011.09.028
- Jakobsen NA, Vyas P. From genomics to targeted treatment in haematological malignancies: a focus on acute myeloid leukaemia. *Clin. Med.* (2018) 18:47. doi: 10.7861/clinmedicine.18-2-s47
- Licht JD, Sternberg DW. The molecular pathology of acute myeloid leukemia. *Hematology.* (2005) 2005:137–42. doi: 10.1182/asheducation-2005.1.137
- Marcotte EL, Spector LG, Mendes-de-Almeida DP, Nelson HH. The prenatal origin of childhood leukemia: potential applications for epidemiology and newborn screening. *Front Pediatr.* (2021) 9:639479. doi: 10.3389/fped.2021.639479
- Baird J, Jacob C, Barker M, Fall CHD, Hanson M, Harvey NC, et al. Developmental origins of health and disease: a life course approach

- to the prevention of non-communicable diseases. *Healthcare*. (2017) 5:14. doi: 10.3390/healthcare5010014
6. Koifman S, Pombo-de-Oliveira MS, Brazilian Collaborative Study Group of Infant Acute Leukemia. High birth weight as an important risk factor for infant leukemia. *Br J Cancer*. (2008) 98:664–7. doi: 10.1038/sj.bjc.6604202
 7. Ma X, Metayer C, Does MB, Buffler PA. Maternal pregnancy loss, birth characteristics, and childhood leukemia (United States). *Cancer Causes Control*. (2005) 16:1075–83. doi: 10.1007/s10552-005-0356-9
 8. Okcu MF, Goodman KJ, Carozza SE, Weiss NS, Burau KD, Bleyer WA, et al. Birth weight, ethnicity, and occurrence of cancer in children: a population-based, incident case-control study in the State of Texas, USA. *Cancer Causes Control*. (2002) 13:595–602. doi: 10.1023/A:1019555912243
 9. Oksuzyan S, Crespi CM, Cockburn M, Mezei G, Kheifets L. Birth weight and other perinatal characteristics and childhood leukemia in California. *Cancer Epidemiol*. (2012) 36:e359–65. doi: 10.1016/j.canep.2012.08.002
 10. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008
 11. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z
 12. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*. (1998) 280:1690–1. doi: 10.1001/jama.280.19.1690
 13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557
 14. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. (1994) 50:1088–101. doi: 10.2307/2533446
 15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629
 16. Xu C, Doi SAR. The robust error meta-regression method for dose-response meta-analysis. *Int J Evidence Based Healthc*. (2018) 16:138–44. doi: 10.1097/XEB.0000000000000132
 17. Hamling J, Lee P, Weitkunat R, Ambuhl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Statist Med*. (2008) 27:954–70. doi: 10.1002/sim.3013
 18. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol*. (1992) 135:1301–9. doi: 10.1093/oxfordjournals.aje.a116237
 19. Cheng W, Zhang Z, Cheng W, Yang C, Diao L, Liu W. Associations of leisure-time physical activity with cardiovascular mortality: a systematic review and meta-analysis of 44 prospective cohort studies. *Eur J Prevent Cardiol*. (2018) 25:1864–72. doi: 10.1177/2047487318795194
 20. Jiménez-Hernández E, Fajardo-Gutiérrez A, Núñez-Enriquez JC, Martín-Trejo JA, Espinoza-Hernández LE, Flores-Lujano J, et al. A greater birthweight increases the risk of acute leukemias in Mexican children-experience from the Mexican Interinstitutional Group for the Identification of the Causes of Childhood Leukemia (MIGICCL). *Cancer Med*. (2018) 7:1528–36. doi: 10.1002/cam4.1414
 21. Schüz J, Forman MR. Birthweight by gestational age and childhood cancer. *Cancer Causes Control*. (2007) 18:655–63. doi: 10.1007/s10552-007-9011-y
 22. Jourdan-Da Silva N, Perel Y, Méchinaud F, Plouvier E, Gandemer V, Lutz P, et al. Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. *Br J Cancer*. (2004) 90:139–45. doi: 10.1038/sj.bjc.6601384
 23. McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS. Birth weight, maternal weight and childhood leukaemia. *Br J Cancer*. (2006) 94:1738–44. doi: 10.1038/sj.bjc.6603173
 24. Barahmani N, Dorak MT, Forman MR, Sprehe MR, Scheurer ME, Bondy ML, et al. Evaluating the role of birth weight and gestational age on acute lymphoblastic leukemia risk among those of Hispanic ethnicity. *Pediatr Hematol Oncol*. (2015) 32:382–9.
 25. Groves FD, Watkins BT, Roberts DJ, Tucker TC, Shen T, Flood TJ. Birth weight and risk of childhood acute lymphoblastic leukemia in Arizona, Illinois, and Kentucky. *South Med J*. (2018) 111:579–84. doi: 10.14423/SMJ.0000000000000873
 26. Roman E, Ansell P, Bull D. Leukaemia and non-Hodgkin's lymphoma in children and young adults: are prenatal and neonatal factors important determinants of disease? *Br J Cancer*. (1997) 76:406–15. doi: 10.1038/bjc.1997.399
 27. Nnattingius S, Zack MM, Ekblom A, Gunnarskog J, Kreuger A, Linet M, et al. Prenatal and neonatal risk factors for childhood lymphatic leukemia. *J Natl Cancer Inst*. (1995) 87:908–14. doi: 10.1093/jnci/87.12.908
 28. Dorak MT, Pearce MS, Hammal DM, McNally RJ, Parker L. Examination of gender effect in birth weight and miscarriage associations with childhood cancer (United Kingdom). *Cancer Causes Control*. (2007) 18:219–28. doi: 10.1007/s10552-006-0093-8
 29. Hjalgrim LL, Rostgaard K, Hjalgrim H, Westergaard T, Thomassen H, Forestier E, et al. Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. *J Natl Cancer Inst*. (2004) 96:1549–56. doi: 10.1093/jnci/djh287
 30. Ou SX, Han D, Severson RK, Chen Z, Neglia JP, Reaman GH, et al. Birth characteristics, maternal reproductive history, hormone use during pregnancy, and risk of childhood acute lymphocytic leukemia by immunophenotype (United States). *Cancer Causes Control*. (2002) 13:15–25. doi: 10.1023/A:1013986809917
 31. Podvin D, Kuehn CM, Mueller BA, Williams M. Maternal and birth characteristics in relation to childhood leukaemia. *Paediatr Perinat Epidemiol*. (2006) 20:312–22. doi: 10.1111/j.1365-3016.2006.00731.x
 32. Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukemia in young children. *Am J Epidemiol*. (2002) 155:603–13. doi: 10.1093/aje/155.7.603
 33. Savitz DA, Ananth CV. Birth characteristics of childhood cancer cases, controls, and their siblings. *Pediatr Hematol Oncol*. (1994) 11:587–99. doi: 10.3109/08880019409141806
 34. Smith A, Lightfoot T, Simpson J, Roman E, UKCCS investigators. Birth weight, sex and childhood cancer: a report from the United Kingdom Childhood Cancer Study. *Cancer Epidemiol*. (2009) 33:363–7. doi: 10.1016/j.canep.2009.10.012
 35. Sprehe MR, Barahmani N, Cao Y, Wang T, Forman MR, Bondy M, et al. Comparison of birth weight corrected for gestational age and birth weight alone in prediction of development of childhood leukemia and central nervous system tumors. *Pediatr Blood Cancer*. (2010) 54:242–9. doi: 10.1002/pbc.22308
 36. Yeazel MW, Ross JA, Buckley JD, Woods WG, Ruccione K, Robison LL. High birth weight and risk of specific childhood cancers: a report from the Children's Cancer Group. *J Pediatr*. (1997) 131:671–7. doi: 10.1016/S0022-3476(97)70091-X
 37. Stacy SL, Buchanich JM, Ma ZQ, Mair C, Robertson L, Sharma RK, et al. Maternal obesity, birth size, and risk of childhood cancer development. *Am J Epidemiol*. (2019) 188:1503–11. doi: 10.1093/aje/kwz118
 38. Paltiel O, Harlap S, Deutsch L, Knaanie A, Massalha S, Tiram E, et al. Birth weight and other risk factors for acute leukemia in the Jerusalem Perinatal Study cohort. *Cancer Epidemiol Biomarkers Prev*. (2004) 13:1057–64.
 39. Heck JE, Lee PC, Wu CK, Tsai HY, Ritz B, Arah OA, et al. Gestational risk factors and childhood cancers: a cohort study in Taiwan. *Int J Cancer*. (2020) 147:1343–53. doi: 10.1002/ijc.32905
 40. Lee J, Chia KS, Cheung KH, Chia SE, Lee HP. Birthweight and the risk of early childhood cancer among Chinese in Singapore. *Int J Cancer*. (2004) 110:465–7. doi: 10.1002/ijc.20159
 41. Murray L, McCarron P, Bailie K, Middleton R, Davey Smith G, Dempsey S, et al. Association of early life factors and acute lymphoblastic leukaemia in childhood: historical cohort study. *Br J Cancer*. (2002) 86:356–61. doi: 10.1038/sj.bjc.6600012
 42. Spracklen CN, Wallace RB, Sealy-Jefferson S, Robinson JG, Freudenheim JL, Wellons MF, et al. Birth weight and subsequent risk of cancer. *Cancer Epidemiol*. (2014) 38:538–43. doi: 10.1016/j.canep.2014.07.004
 43. Westergaard T, Andersen PK, Pedersen JB, Olsen JH, Frisch M, Sørensen HT, et al. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. *J Natl Cancer Inst*. (1997) 89:939–47. doi: 10.1093/jnci/89.13.939

44. Wiemels JL, Xiao Z, Buffler PA, Maia AT, Ma X, Dicks BM, et al. *In utero* origin of t(8;21) AML1-ETO translocations in childhood acute myeloid leukemia. *Blood*. (2002) 99:3801–5. doi: 10.1182/blood.V99.10.3801
45. Baik I, Devito WJ, Ballen K, Becker PS, Okulicz W, Liu Q, et al. Association of fetal hormone levels with stem cell potential: evidence for early life roots of human cancer. *Cancer Res*. (2005) 65:358–63.
46. Michels KB, Xue F. Role of birthweight in the etiology of breast cancer. *Int J Cancer*. (2006) 119:2007–25. doi: 10.1002/ijc.22004
47. Trichopoulos D, Lipworth L. Is cancer causation simpler than we thought, but more intractable? *Epidemiology*. (1995) 6:347–9. doi: 10.1097/00001648-199507000-00003
48. Peters JM, Preston-Martin S, London SJ, Bowman JD, Buckley JD, Thomas DC. Processed meats and risk of childhood leukemia (California, USA). *Cancer Causes Control*. (1994) 5:195–202. doi: 10.1007/BF01830266
49. Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW, et al. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ*. (2013) 346:f3443. doi: 10.1136/bmj.f3443
50. McCormack VA, dos Santos Silva I, Koupil I, Leon DA, Lithell HO. Birth characteristics and adult cancer incidence: Swedish cohort of over 11,000 men and women. *Int J Cancer*. (2005) 115:611–7. doi: 10.1002/ijc.20915
51. Ruder EH, Dorgan JF, Kranz S, Kris-Etherton PM, Hartman TJ. Examining breast cancer growth and lifestyle risk factors: early life, childhood, and adolescence. *Clin Breast Cancer*. (2008) 8:334–42. doi: 10.3816/CBC.2008.n.038

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