OSJ OPEN SCIENCE JOURNAL

REVIEW

Association between Birthweight and Acute Lymphoblastic Leukemia in Children, a Systematic Review

Livingstone Aduse-Poku[1]*, Samuel Akyirem[2]

[1]University of Florida, United States of America
[2]Kings College, United Kingdom

*Corresponding author: Livingstone Poku: Adusepokulivingstone@gmail.com

OPEN ACCESS

Citation: Aduse-Poku L.,Akyirem S. (2020) Association between Birthweight and Acute Lymphoblastic Leukemia in Children, a Systematic Review. Open Science Journal 5(3)

Received: 18th March 2020

Accepted: 13th August 2020

Published: 18th September 2020

Funding: The author received no specific funding for this work

Competing Interests: The author has declared that no competing interests exist.

Abstract:

Background: Birthweight is normally determined by a range of genetic traits and exposures occurring within the intra-uterine environment. Some epidemiological studies have reported high birthweight as a risk factor of Acute lymphoblastic Leukemia (ALL). Other studies have however not demonstrated this relationship.

Objectives: The objective of this review is to assess the association between birthweight and Acute Lymphoblastic Leukemia in children.

Search methods: We searched observational studies from Cochrane, MEDLINE, EMBASE, ISI Web of Science, BIOSIS, the allied and Complementary Medicine Database and National Research Register, ClinicalTrial.gov, WHO International Trials Registry Platform.

Selection criteria: We included case control and cohort studies assessing the association between birthweight and ALL in children. All participants below the age of 18 years (children) with Acute Lymphoblastic Leukemia (ALL) were included in the analysis. The independent variable in this review was birth weight. Birthweight was categorized into two (2): Birthweight >4kg (experimental arm) and ≤4kg (control arm).

Data collection and analysis: Two reviewers independently assessed identified studies through two stages of screening. First, titles and abstracts of all references identified through searches were screened and irrelevant studies were excluded. Also, full texts of potentially eligible studies were further assessed according to previously defined inclusion criteria were excluded and reasons for their exclusion were stated. All studies that met

the inclusion criteria were included. Areas of disagreement were resolved by a third-party review. Two review authors double checked the studies independently.
Main results:Out of the 348 studies screened, 16 of them met the inclusion criteria. A total of 3,650,728 participants provided data for analysis in this review. These studies were published between 1987 and 2018. The age span of studies was similar across studies (roughly (0-18 years). The vast majority of ALL was diagnosed before 15 years. 14 of the included studies were case control studies and 2 of them were cohort studies. Figure 1 presents odd ratio estimates for effect of birthweight on ALL ($\leq$ 4000g vs. $>$ 4000g). There was a statistically significant positive relationship between high birthweight (birthweight $>$ 4000g) and risk of ALL (16 studies, OR 0.81, 95% CI 0.77, 0.85).
Authors' conclusions:Our study revealed a significant positive relationship between high birthweight and ALL. Several studies have demonstrated an association between factors such as: high pre-pregnancy weight and height; gestational age greater than 42 weeks; parity greater than and high birthweight. Therefore, public health programs and interventions aimed at reducing the incidence of these maternal factors can reduce the risk of high birthweight and lower the incidence of ALL.

Keywords: Birthweight, Acute Lymphoblastic Leukemia, Children, Cancer.

Introduction

Leukemia is a heterogeneous group of blood-forming cancers that comprise several biologically distinct sub-groups. It accounts for 2.6% of all cancers worldwide with 437,033 new cases diagnosed in 2018. (American Institute for Cancer Research, 2019) An estimated 176,200 people in the United States were expected to be diagnosed with Leukemia, lymphoma and myeloma in 2019, which would account for 10% of new cases of cancer (American Cancer Society, 2019). Leukemias, the most common cancer in children, account for almost 1 out of 3 cancers worldwide (Gatta et al., 2014). About 3 out of 4 leukemias in children and teens are Acute Lymphocytic Leukemia (ALL; Gatta et al., 2014).

Several genetic and environmental risk factors have been implicated in the pathogenesis of ALL (Petridou et al., 2002). Leukemia development begins with cellular mutation, usually chromosomal translocation, during embryogenesis (Greaves 2002; Rossig & Juergens, 2008). Cells with certain chromosomal translocation such as t(12;21), (4;11) or t(8;21) are frequently found at birth in children who later develop leukemia (Greaves, 2005; WIemels et al. 2002). Moreover, there is some evidence that perinatal exposures may pose risk for ALL in children. A recent meta-analysis of original studies from the Childhood

Leukemia International Consortium have showed positive associations between home paint (Bailey et al. 2015), occupational pesticides (Bailey et al. 2014), maternal supplementation of folic (Mateyer, 2014) and acute lymphoblastic leukemia.

A commonly investigated risk factor of ALL is birthweight. The observation that heavy babies (variously defined as weighing more than 3500g, 4000g and 4500g) are at risk of developing ALL has received a lot of attention (Johnson, Soler, Puumala, Ross & Spector, 2008; Caughey & Michels, 2009; Smith, Lightfoot, Simpson, & Roman, 2009). Higher birthweight is associated with maternal and fetal hyperglycemia as well as elevated blood insulin levels – all of which are factors that are linked with a higher risk of ALL (McLaughlin, Baptiste, Schymura, Nasca, & Zdeb, 2006; Caughey & Michels, 2009).

Some studies have estimated that the risk of ALL increases by 25% for children with birthweight of more than 4000g (Hjalgrim et al, 2003). Other studies have also reported the following odds ratios per kilogram increase in birthweight: 1.45 (Westergaard et al. 1997); 1.29 (Petridou et al. 1997); 1.03 (Shuz et al 1999) and 1.09 (Shu et al. 2002). The evidence on birthweight and ALL has however been inconsistent, with other studies failing to establish significant relationship between birthweight and ALL (Reynolds, Behren & Elkin, 2002; Mckinney et al. 1999; Roman Ansell & Bull, 1997).

Pooled evidence from various meta-analyses are suggestive of low to moderate positive association between ALL and birthweight (Hjalgrim et al, 2003). However, the most recent meta-analysis we found was conducted more than a decade ago (Caughey & Michels, 2009). In light of recent evidence from empirical studies, it is important that this association between birthweight and ALL is re-examined We therefore, conducted a systematic review of available clinical evidence to date to assess the influence of normal and high birthweight on the risk of ALL.

Methods

Inclusion and exclusion criteria

We included case control and cohort studies that a) assessed the association between birthweight (independent variable) and ALL (outcome variable) b) used participants aged below 18 years c) reported the number of ALL cases using two categories of birthweight, i.e., >4kg (high) and ≤4kg (normal) based on the World Health Organization's (WHO) classification of birthweight d) were written in English. Studies with no abstract were excluded. We also excluded studies that reported birthweight as a continuous variable only and not as our predefined categories of high and normal birthweight.

Search methods for identification of studies

An electronic search was conducted on 6th October 2019 on the following databases: Cochrane, MEDLINE, EMBASE, ISI Web of Science, BIOSIS, the allied and Complementary Medicine Database and National Research Register, ClinicalTrial.gov, and WHO International Trials Registry Platform. Search terms included variants of "acute lymphocytic leukemia OR ALL" AND "birthweight". Full details of search terms can be found in, Table 2. The search strategy was

adapted for each electronic database by using database-specific index terms. We also hand-searched reference lists from published studies, bibliographies of relevant systematic reviews and grey literature sources such as dissertations, theses and google scholar.

Selection of studies

The results of the electronic search were imported into Covidence (https://www.covidence.org). Two reviewers (SA and LA) independently assessed identified studies through two stages of screening. Firstly, titles and abstracts of all references were screened, and irrelevant studies were excluded. Secondly, full texts of tentatively eligible studies were further assessed against the pre-defined inclusion criteria. Areas of disagreement were resolved through discussions between the two reviewers and the reaching of consensus. The use of two independent reviewers ensured objectivity and transparency in the selection and synthesis of evidence.

Data extraction and risk of bias assessment

Data on study design, sample characteristics, exposure and outcomes were extracted independently by the two reviewers using the default data extraction form in Covidence. The extracted data were then transferred from Covidence to Review Manager 5 software for meta-analysis. We also assessed the methodological quality of included studies using the Critical Appraisal Skills Program (CASP) for case control and cohort studies as appropriate. The CASP checklist for case control and cohort studies are 11- and 12-items checklists that enable the reviewer to assess the methodological rigor and validity and reliability of evidence from case-control and cohort studies respectively.

Data synthesis

Since all our outcomes were dichotomous, we used odds ratios (OR) as our effect measure. Narrative synthesis was used to summarize the key findings of included studies. Outcome data from included studies were pooled for meta-analysis using the fixed effects model. We used the inverse variance method to estimate the combined effect size for the outcomes in the meta-analysis. We evaluated the statistical heterogeneity in the data using the I2 statistic (Higgins, 2003). We also evaluated clinical heterogeneity of included studies by assessment of study population characteristics. Funnel plots was used to assess reporting (publication) bias. We assessed funnel plots visually and used formal tests for funnel plot asymmetry.

Findings

Results of the search

The search on all electronic databases produced a total of 348 records, of which 187 were duplicates. The remaining 169 studies were screened for titles and abstracts and 129 records were found ineligible for the review. Sixteen other

studies were excluded after full text screening. The remaining 16 studies that met the eligibility criteria were included in the current review (Figure 3)

Characteristics of included studies

A total of 3,650,728 participants provided data for analysis in this review. The studies originated from the USA (n=9), Australia, Germany, Azerbaijan, Denmark, Mexico, Sweden and Brazil. The studies were published between 1987 and 2018. The age span of studies was similar across studies (roughly 0-18 years). The vast majority of ALL was diagnosed before 15 years. Thirteen of the included studies were case control studies and 3 of them were cohort studies.

Synthesis of evidence

Figure 1 presents odds ratio estimates for effect of birthweight on ALL ($\leq$ 4000g vrs $>$ 4000g). All but six of the included studies individually showed a statistically significant positive relationship between high birthweight (birthweight $>$ 4000g) and ALL. Evidence from the fixed effect meta-analysis model suggests 24% higher odds of ALL with children whose birthweight exceeds 4000g (N=16, OR 1.24, 95% CI 1.18, 1.34). The quality of evidence was rated moderate as the average of total for all domains of included studies was 13.5 (Table 1).

Discussion

We analyzed 16 epidemiologic studies of the association between birthweight and Acute Lymphoblastic Leukemia, including information on about 17155 children with Leukemia. The analysis demonstrated a significant increase of ALL in children with high birthweight ($\leq$4000g vrs $>$4000g), corresponding to an odd ratio of 0.81 (CI: 0.77-0.85). The association between birthweight and risk of Leukemia was consistently observed in the studies conducted over a period of more than 30 years.

A previous meta-analysis conducted by Hjalgrim et al. (2003) also found a similar positive association for high birthweight and Acute Lymphoblastic Leukemia, reporting ($>$4000g vs. $\leq$ 4000g), odd ratio of 1.26 (CI: 1.17-1.37). Also, our result is consistent with the findings of Caughey & Michels, (2009) who found a non-significant positive association between high birthweight and ALL in children, (OR, 1.23 (95% CI: 1.15, 1.32). The article by Gholami, 2003 identified a relatively strong association between birth weight and ALL risk (corresponding to an OR, 0.45, (95% CI: 0.24, 0.86).

Various studies have shown that genetic events such as chromosomal translocation initiated in-utero can lead to acute leukemias (Ford at al., 1993; Gill et al. 1994; Wiemels, Ford, Van & Postma, 1999). Ultimately this process leads to the uncontrolled proliferation and accumulation of a single clone of immature lymphoblasts (Greaves, 1999) Birth weight has been associated with several growth factors such as insulin-like growth factor I (IGF I), insulin-like growth factor II (IGF-II) and sex-steroid hormones (Michels & Xue, 2006). Growth factors may increase the number of stem cells in utero, which increases the total number of replicating cells at risk for conversion into tumor cells, leading to leukemias (Trichopoulos & Lipworth, .1995). In addition, high birthweight resulting from high levels of growth factors in-utero may increase the

risk of ALL by inducing proliferative stress on the bone marrow (Ross et al. 1996; Albanes & Winick, 1988).

In summary, this study confirms previously reported evidence of a positive association between high birth weight and overall leukemia risk. This result emphasizes the need for studies to clarify the biologic mechanisms underlying the association between birthweight and ALL.

Conclusion

Our study revealed a significant positive relationship between high birthweight and ALL. Several studies have demonstrated an association between factors such as: high pre-pregnancy weight and height (Janne, Tine, Ulrik & Niels, 2003); gestational age greater than 42 weeks (Ceska, 2005); parity greater than 2 (Wikstrom, Axelsson , & Bergstrom, 1991) and high birthweight. Therefore, public health programs and interventions aimed at reducing the incidence of these maternal factors will help reduce the incidence of ALL.

References:

American Cancer Society's Cancer Facts & Figures. https://www.cancer.org/research/cancer-facts-statistics.html. 2019.

American Institute for Cancer Research. World Cancer Data. Global Statistics for the most common cancers. 2019. https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data.

Bailey HD, Fritschi L, Infante-Rivard C. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the Childhood Leukemia International Consortium. Int J Cancer. 2014;135(9):2157–2172.

Bailey HD, Metayer C, Milne E, et al. Home paint exposures and risk of childhood acute lymphoblastic leukemia: findings from the Childhood Leukemia International Consortium. Cancer Causes Control. 2015;26(9):1257–1270

Bernbeck B, et al. Symptoms of childhood acute lymphoblastic leukemia: red flags to recognize leukemia in daily practice. Klin Padiatr 2009;221:369–73. doi:10.1055/s-0029-1239538.

Biswas S, et al. Childhood acute leukemia in West Bengal, India with an emphasis on uncommon clinical features. Asian Pac J Cancer Prev 2009;10:903–6.

Caughey RW, Michels KB. Birth weight and childhood leukemia: a meta-analysis and review of the current evidence. Int J Cancer 2009;124(11):2658–70.

Clarke RT, et al. Clinical presentation of childhood leukaemia: a systematic review and meta-analysis. Archives of Disease in Childhood 2016;101:894-901.

Gatta G et al. Childhood cancer survival in Europe 1999 - 2007: results of EUROCARE - 5−a population - based study. Lancet Oncol. 2014;15:35 - 47.

Greaves M. In utero origins of childhood leukaemia. Early Hum Dev 2005;81(1):123–9.

Hjalgrim LL, Madsen HO, Melbye M, et al. Presence of clonespecific markers at birth in children with acute lymphoblastic leukaemia. Br J Cancer 2002;87:994–9.

McKinney PA, Juszczak E, Findlay E, et al. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: a Scottish case control study. Br J Cancer 1999;80:1844–51.

McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS. Birth weight, maternal weight and childhood leukaemia. Br J Cancer 2006;94(11):1738–44.

Metayer C, Dahl G, Wiemels J, Miller M. Childhood Leukemia: A Preventable Disease. 2016. Pediatrics, 138(Suppl 1), S45-S55.

Metayer C, Milne E, Dockerty JD. Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: a Childhood Leukemia International Consortium study. Epidemiology. 2014;25(6):811–822

Reynolds P, Behren JV, Elkin EP. Birth characteristics and leukemia in young children. Am J Epidemiol 2002;155:603–13.

Robazzi TC, Barreto JH, Silva LR, Osteoarticular manifestations as initial presentation of acute leukemias in children and adolescents in Bahia, Brazil. J Pediatr Hematol Oncol 2007;29:622–6. doi:10.1097/MPH.0b013e3181468c55.

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.

Smith A, Lightfoot T, Simpson J, Roman E. Birth weight, sex and childhood cancer: a report from the United Kingdom childhood cancer study. Cancer Epidemiol 2009;33(5):363–7.

Sprehe MR, Barahmani N, Cao Y, 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(2):242–9.

Wiemels JL, Xiao Z, Buffler PA, et al. In utero origin of t(8;21) AML1-ETO translocations in childhood acute myeloid leukemia. Blood 2002;99:3801–5.

Barahmani N, Dorak MT, Forman, Michele RS, Michael E, Bondy ML, Okcu MF, Lupo, PJ. Evaluating the Role of Birth Weight and Gestational Age on Acute Lymphoblastic Leukemia Risk Among Those of Hispanic Ethnicity.. Pediatric Hematology And Oncology 2015;32(6):382-389.

Crump C, Sundquist J, Sieh W, Winkleby MA, Sundquist K. Perinatal and familial risk factors for acute lymphoblastic leukemia in a Swedish national cohort.. Cancer (0008543X) 2015;121(7):1040-1047. [DOI: 10.1002/cncr.29172]

Gholami A, Salarilak S, Hejazi S, Khalkhali HR. Birth weight and risk of childhood acute leukaemia.. Eastern Mediterranean Health Journal = La Revue De Sante De La Mediterranee Orientale = Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit 2013;19(2):156-161.

Hjalgrim LL, Rostgaard Klaus, Hjalgrim H, Westergaard T, Thomassen H, Forestier E, Gustafsson G, Kristinsson J, Melbye M, Schmiegelow Kjeld. Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. Journal Of The National Cancer Institute 2004;96(20):1549-1556.

Jiménez-Hernández, 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 Medicine 2018;7(4):1528-1536. [DOI: 10.1002/cam4.1414].

Koifman S, Pombo-de-Oliveira MS. High birth weight as an important risk factor for infant leukemia.. British Journal Of Cancer 2008;98(3):664-667. [DOI: 10.1038/sj.bjc.6604202]

McLaughlin, C C; Baptiste, M S; Schymura, M J; Nasca, P C; Zdeb, M S. Birth weight, maternal weight and childhood leukaemia.. British Journal Of Cancer 2006;94(11):1738-1744.

Milne E, Royle JA. de Klerk NH, Blair E, Bailey H, Cole C, Attia J, Scott RJ, Armstrong BK. Fetal growth and risk of childhood acute lymphoblastic leukemia: results from an Australian case-control study.. American Journal Of Epidemiology 2009;170(2):221-228. [DOI: 10.1093/aje/kwp117]

Okcu MF, Goodman, Karen J, Carozza SE, Weiss NS, Burau KD, Bleyer WA, Cooper SP. 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: CCC 2002;13(7):595-602. [DOI:]

Oksuzyan S, Crespi CM, Cockburn M, Mezei G, Kheifets L. Birth weight and other perinatal characteristics and childhood leukemia in California.. Cancer Epidemiology 2012;36(6):e359-e365. [DOI: 10.1016/j.canep.2012.08.002]

Ou SX, Han DS, Richard K, Chen Z, Neglia JP, Reaman GH, Buckley JD, Robison LL. Birth characteristics, maternal reproductive history, hormone use during pregnancy, and risk of childhood acute lymphocytic leukemia by immunophenotype (United States).. Cancer Causes & Control: CCC 2002;13(1):15-25.

Podvin D, Kuehn CM, Mueller BA, Williams M. Maternal and birth characteristics in relation to childhood leukaemia.. Paediatric And Perinatal Epidemiology 2006;20(4):312-322.

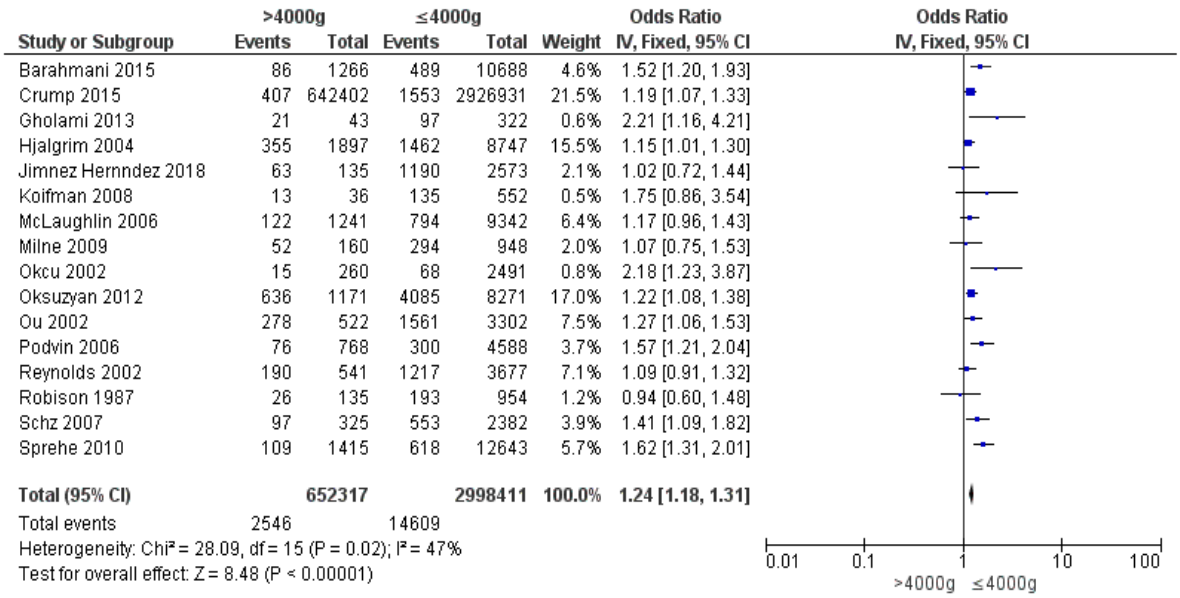
Reynolds P, Von B, Julie Elkin, Eric P. Birth characteristics and leukemia in young children. American Journal Of Epidemiology 2002;155(7):603-613.

Robison LL, Codd M, Gunderson P, Neglia JP, Smithson WA, King FL. Birth weight as a risk factor for childhood acute lymphoblastic leukemia. Pediatric Hematology And Oncology 1987;4(1):63-72.

Schüz Joachim; Forman, Michele R. Birthweight by gestational age and childhood cancer.. Cancer Causes & Control: CCC 2007;18(6):655-663.

Sprehe MR, Barahmani, Nadia CY, Wang T, Forman, Michele R, Bondy M, Okcu MF. Comparison of birth weight corrected for gestational age and birth weight alone in prediction of development of childhood leukemia and central nervous system tumors.. Pediatric Blood & Cancer 2010;54(2):242-249. [DOI: 10.1002/pbc.22308]

Figures



Caption

Forest plot of comparison: 3 >4000g vrs ≤4000g, outcome: 3.1 Acute Lymphoblastic Leukemia.

Forest plot of comparison: 1 >4000g vs ≤4000g, outcome: 1.2 New Outcome.

Figure 1 (Analysis 1.2)

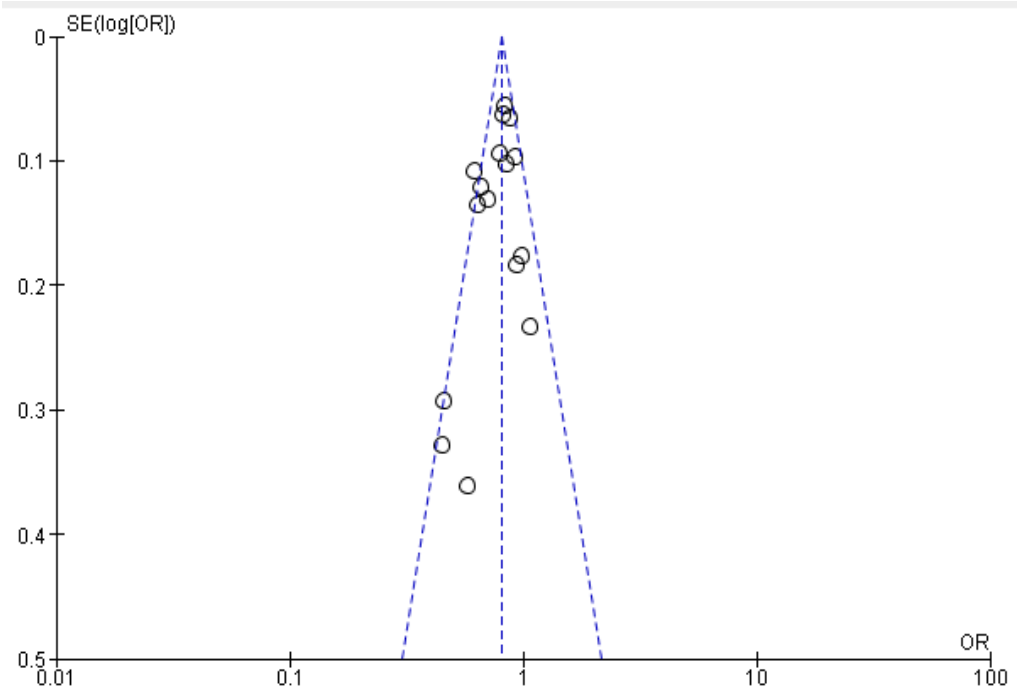


Figure 2- Funnel plot.

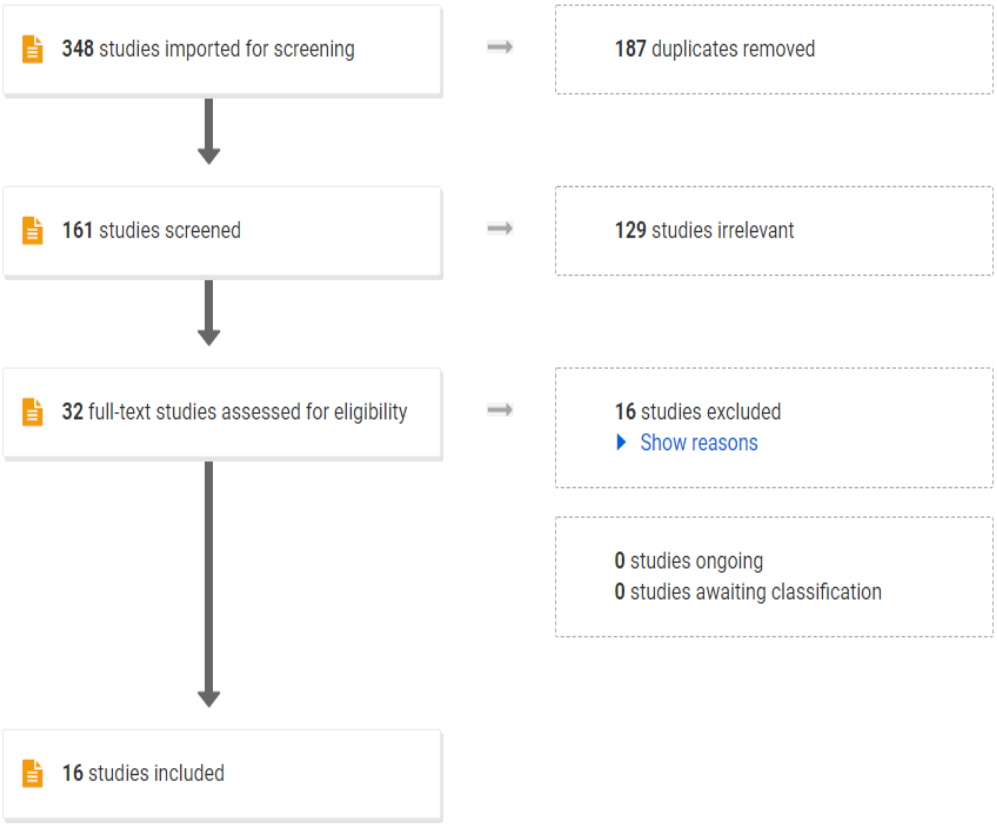


Figure 3: Prisma table

Tables

Table 1. Downs and Black Checklist for Included Studies

Studies and domains	Barahmani 2015	Crump 2015	Gholami 2013	Hjalgrim 2004	Jiménez-Hernández 2018	Koifman 2008	McLaughlin 2006	Milne 2009
Aim clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcomes clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patients characteristics clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Interventions clearly described?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Principal confounders clearly described?	Yes	Yes	No	No	Yes	Yes	No	Yes
Main findings	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

clearly described?								
Random variability for main outcome provided?	No	No	No	No	Yes	No	No	No
Adverse events reported?	No	No	No	No	Yes	No	No	No
Loss-to-follow up reported?	No	No	No	No	No	No	Yes	No
Actual p-value reported?	Yes	Yes	Yes	Yes	No	Yes	No	No
Sample asked to participate representative of the population?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Sample agreed to participate representative of the population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Staff participating representative of the patients' environment?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Attempt to blind participants?	No	No	No	Yes	No	No	No	No
Attempt to blind assessors?	No	No	No	Yes	No	No	No	No
Data dredging results stated clearly?	No	No	Yes	No	No	Yes	Yes	Yes
Analysis adjusted for length of follow up?	No	Yes	No	Yes	No	No	No	No
Appropriate statistics?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reliable compliance?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Accurate outcome measures?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Same population?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Participants recruited at the same time?	Yes	No	No	No	No	No	No	Yes

Randomised?	No	No	No	No	No	No	No	No
Adequate allocation concealment?	No	No	No	Yes	No	No	No	No
Adequate adjustment for confounders?	Yes	No	No	No	No	Yes	Yes	Yes
Loss of follow up reported?	No	Yes	No	No	Yes	No	Yes	No
Power calculation?	No	No	No	No	Yes	No	No	No
Total score: (sum of all domains)	14	14	11	14	15	14	14	14

Studies and domains	Okcu 2002	Oksuzyan 2012	Ou 2002	Podvin 2006	Reynolds 2002	Robison 1987	Schüz 2007	Sprehe 2010
Aim clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcomes clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patients characteristics clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Interventions clearly described?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Principal confounders clearly described?	No	Yes	No	Yes	No	No	Yes	No
Main findings clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Random variability for main outcome provided?	No	No	No	No	No	Yes	No	No
Adverse events reported?	No	No	No	No	No	No	No	No
Loss-to-follow up reported?	No	No	Yes	No	No	No	No	Yes
Actual p-value reported?	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Sample asked to participate representative of the population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample agreed to participate representative of the population?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Staff participating representative of the patients' environment?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Attempt to blind participants?	No	No	No	No	No	No	No	No
Attempt to blind assessors?	No	No	No	No	No	No	No	No
Data dredging results stated clearly?	No	Yes	Yes	No	No	No	No	No
Analysis adjusted for length of follow up?	No	No	No	No	No	No	No	No
Appropriate statistics?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reliable compliance?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Accurate outcome measures?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Reliable compliance?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Accurate outcome measures?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Same population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Participants recruited at the same time?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Randomised?	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Adequate allocation concealment?	No	Yes	Yes	Yes	Yes	No	Yes	No
Adequate adjustment for confounders?	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Loss of follow up reported?	No	No	Yes	No	No	No	No	No
Power calculation?	Yes	Yes	No	No	No	No	No	No
Total score: (sum of all domains)	15	17	18	15	15	12	15	13

NB: Yes= 1, No = 0, Average of all domains of included studies = 13.5

Table 2. List and Combination of Search Terms

1. Acute
2. Leukemia
3. Lymphocytic
4. Birth
5. Children
6. Weight
7. Systematic review
8. Lymphoma
9. Myeloma
10. Infants
11. Childhood
12. Observational
13. Case-controlled
14. Cross-sectional studies
15. 1+3+2+5+6
16. 2+5+4+6

17. 4+7+11
18. 3 or 2 or 5 or 12
19. 6 or 9 or 5 or 4

Characteristics of studies

Characteristics of included studies

Barahmani 2015

Methods	Study design: Case control study Study grouping: Case and control
Participants	Baseline Characteristics Included criteria: . The authors compared birth certificate data of 575 children diagnosed with ALL who were younger than 5 years and included in the Texas Cancer Registry, Texas Department of Health, between the years 1995 and 2003 with 11,379 controls matched by birth year. Excluded criteria: Gestational age (GA) and/or BW missing or if BW was less than 500 g
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome Reporting: Fully reported Direction: Lower is better
Identification	Sponsorship source: Not reported Country: United States of America Setting: Texas Department of State Health Services Comments: Authors name: Nadia Barahmani,Tevfik Dorak, Michele R. Forman, Michael Sprehe, Michael E. Scheurer, Melissa L. Bondy, Fatih Okcu,and Philip J. Lupo Institution: Department of Pediatrics, Baylor College of Medicine, Texas Children's Cancer Center, Houston, Texas, USA; 2Childhood Cancer Prevention and Epidemiology Center, Houston, Texas, USA; Email: Philip.Lupo@bcm.edu Address: One Baylor Plaza, Houston, TX 77030
Notes	

Crump 2015

Methods	Study design: Cohort study
Participants	Baseline Characteristics Included criteria: Individuals in the Swedish Birth Registry who were born from 1973 through 2008 Excluded criteria: Individuals with Down syndrom, others who had missing information for birth weight, and others who had missing information for gestational age at birth. Pretreatment:
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome
Identification	Sponsorship source: This work was supported by the National Cancer Institute at the National Institutes of Health [grant number R03 CA171017]; the Swedish Research Council; and ALF project grant, Region Skåne/Lund University, Sweden. Country: Sweden Setting: Center for Primary Health Care Research, Lund University, Malmö, Sweden Authors name: Casey Crump, Jan Sundquist, Weiva Sieh, Marilyn A. Winkleby, and Kristina Sundquist. Institution: Center for Primary Health Care Research, Lund University, Malmö, Sweden Email: kccrump@stanford.edu. Address: Stanford University, Department of Medicine, 211 Quarry Road, Suite 405, MC 5985, Palo Alto, California USA 94304-1426.
Notes	

Gholami 2013

Methods	Study design: Case control study Study grouping: Participants with ALL and those without ALL
Participants	Baseline Characteristics Included criteria: Patients with acute leukaemia, diagnosed from 20 March 2003 and 20 March 2009, age less than 15 years at the time of diagnosis and residing in West Azerbaijan province at the time of diagnosis
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome
Identification	Sponsorship source: National Cancer Institute at the National Institutes of Health [grant number R03 CA171017]; the Swedish Research Council; and ALF project grant, Region Skåne/Lund University, Sweden Country: Sweden Setting: Swedish Birth Registry Authors name: Casey Crump, Jan Sundquist, Weiva Sieh, Marilyn A. Winkleby, and Kristina Sundquist. Institution: Center for Primary Health Care Research, Lund University, Malmö, Sweden Email: kccrump@stanford.edu

	Address: Stanford University, Department of Medicine, 211 Quarry Road, Suite 405, MC 5985, Palo Alto, California USA 94304-1426.
Notes	

Hjalgrim 2004

Methods	Study design: Case Controlled study Study grouping: Case and control
Participants	Baseline Characteristics Included criteria: Patients who have been diagnosed with Acute Lymphoblastic Leukemia Excluded criteria: Patients with down syndrome Pretreatment:
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome
Identification	Sponsorship source: Not stated Country: Denmark Setting: Danish Epidemiology Science Center, Statens Serum Institut, Copenhagen, Denmark. Authors name: Lisa Lyngsie Hjalgrim, Klaus Rostgaard, Henrik Hjalgrim, Tine Westergaard, Harald Thomassen, Erik Forestier, Göran Gustafsson, Jon Kristinsson, Mads Melbye, Kjeld Schmiegelow. Institution: Department of Epidemiology Research, Danish Epidemiology Science Center, Statens Serum Institut, Copenhagen, Denmark. Email: : lih@ssi.dk. Address: Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark
Notes	

Jimnez Hernndez 2018

Methods	Study design: Case-control study Study grouping:
Participants	Baseline Characteristics Included criteria: incident cases with acute lymphoblastic leukemia (ALL) diagnosed between 2010 and 2015. Excluded criteria: Not indicated
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome
Identification	Sponsorship source: Consejo Nacional de Ciencia y Tecnologia [grant numbers: SALUD-2010-1-141026, FIS/ IMSS/PROT/895; PDCPN2013-01-215726, FIS/IMSS/PROT/1364; SALUD 2015-1- 262190, FIS/IMSS/PROT/1533 and CB-2015-1-258042, FIS/IMSS/PROT/1548] and by the Instituto Mexicano del Seguro Social

	[grant numbers: FIS/IMSS/PROT/ PRIO/11/017, FIS/IMSS/PROT/G12/1134. Country: Mexico Setting: Public hospitals of Mexico City Authors name: Elva Jiménez-Hernández, Arturo Fajardo-Gutiérrez, Juan Carlos Núñez-Enriquez, Jorge Alfonso Martín-Trejo, Laura Eugenia Espinoza-Hernández. Institution: Instituto Mexicano del Seguro Social (IMSS), Mexico City, Mexico Email: juan.mejiaa@imss.gob.mx Address: Cuauhtémoc 330, Delegación Cuauhtémoc, Ciudad de México, 06720 México.
Notes	

Koifman 2008

Methods	Study design: Case-controlled study
Participants	Baseline Characteristics ≤4000g >4000g Overall Included criteria: Patients diagnosed with Acute Lymphoblastic Leukemia whose birthweights are available. Excluded criteria: Cases with no birthweight record Pretreatment:
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome
Identification	Sponsorship source: Not stated Country: Brasil Setting: Different hospitals in Brasil Authors name: S Koifman1 and M.S Pombo-de-Oliveira Institution: Divisa˜o de Medicina Experimental, Centro de Pesquisa – Instituto Nacional De Caˆncer, Rio de Janeiro, Rua Andre´ Cavalcanti, 37, CEP, Rio de Janeiro, RJ 20231-050, Brazil Email: mpombo@inca.gov.br
Notes	

McLaughlin 2006

Methods	Study design: Cohort study Study grouping:
Participants	Baseline Characteristics Included criteria: All cases age 1 month to 9 years diagnosed with acute leukemia between 1985 and 2001 while resident of New York State and born in New York State Excluded criteria: Cases born in New York city
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome

Identification	Sponsorship source: Not reported Country: United States of America Setting: e New York State Cancer Registry Comments: Authors name: CC McLaughlin, MS Baptiste,MJ Schymura, PC Nasca4 and MS Zdeb Institution: New York State Cancer Registry, New York State Department of Health. Email: ccm01@health.state.ny.us Address: Empire State Plaza, Albany, NY 12237-0679, USA.
Notes	

Milne 2009

Methods	Study design: Case-control study
Participants	Baseline Characteristics Included criteria: Cases (Acute Lymphoblastic Leukemia patients) were eligible to participate if they were diagnosed between July 1, 2003, and December 31, 2006 Excluded criteria: Children with birth defects—including Down syndrome.
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome
Identification	Sponsorship source: Australian National Health and Medical Research Council (grant ID 254539). E. Milne is supported by an NHMRC Career Development Award and Cancer Council Western Australia Research Fellowship. B. Armstrong's research is supported by a University of Sydney Medical Foundation Program Grant. H. Bailey is supported by an NHMRC PhD Scholarship. Country: Australia Setting: oncology centers in Australia, where virtually all children with ALL are treated Comments: Authors name: E. Milne, J. A. Royle, N. H. de Klerk, E. Blair, H. Bailey, C. Cole, J. Attia, R. J. Scott, and B. K. Armstrong Institution: Telethon Institute for Child Health Research Email: lizm@ichr.uwa.edu.au) Address: Telethon Institute for Child Health Research, P.O. Box 855, Perth, Western Australia, 6872
Notes	

Okcu 2002

Methods	Study design: Case-controlled study Study grouping:
Participants	Baseline Characteristics ≤4000g >4000g Overall Included criteria: children younger than five years of age who were residents of Texas, diagnosed with cancer in 1995 and registered bythe Texas Cancer Registry (TCR) of the Texas Department of Health (TDH). Excluded criteria: Birthweights less than 1000g

Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome
Identification	Sponsorship source: Not reported Country: USA Setting: Texas Cancer Registry (TCR) of the Texas Department of Health (TDH). Comments: Authors name: Mehmet Fatih Okcu, Karen J. Goodman, Susan E. Carozza, Nancy S. Weiss, Keith D. Burau, W. Archie Bleyer & Sharon P. Cooper Institution: Division of Pediatrics, University of Texas Email: fokcu@mdanderson.org Address: Division of Pediatrics, Box 087, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA.
Notes	

Oksuzyan 2012

Methods	Study design: Case-controlled study Study grouping:
Participants	Baseline Characteristics Included criteria: Childhood leukemia cases diagnosed between 1988 and 2008 in children younger than 16 years who were born in California and resided in California at the time of diagnosis Excluded criteria: Not reported
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome
Identification	Sponsorship source: Not reported Country: USA Setting: California Cancer Registry Authors name: S. Oksuzyan, C.M. Crespi b , M. Cockburn, G. Mezei d , L. Kheifets. Institution: California Cancer Registry Email: soksuzyan@ucla.edu
Notes	

Ou 2002

Methods	Study design: Case-control study
Participants	Baseline Characteristics 1842 ALL cases (age <15 years) Included criteria: 1842 ALL cases (age <15 years) Excluded criteria: Ineligible matched case
Interventions	Intervention Characteristics ≤4000g >4000g

Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous Outcome
Identification	Sponsorship source: University of Minnesota Children's Research Fund and grants no. CA49450 and CA58051 from the National Cancer Institute. Country: USA Setting: California Authors name: Xiao Ou Shu, Dehui Han, Richard K. Severson, Zhi Chen, Joseph P. Neglia, Gregory H. Reaman , Jonathan D. Buckley & Leslie L. Robison Institution: Children Cancer Group Email: Address: XiaoOu.Shu@mcmail. vanderbilt.edu
Notes	

Podvin 2006

Methods	Study design: Case-controlled study Study grouping:
Participants	Baseline Characteristic Included criteria: Children , 20years diagnosed with ALL Excluded criteria: Infants with Down's syndrome
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous Outcome
Identification	Sponsorship source: Cancer Surveillance System of the Fred Hutchinson Cancer Research Center Country: United States of America Setting: Washington State Cancer Registry Comments: Authors name: Danise Podvina, Carrie M. Kuehna, Beth A. Muellera, and Michelle Williams Institution: University of Washington, Department of Rehabilitation Medicine, Centre for Technology and Disability Studies Email: cmkuehn@u.washington.edu Address: Centre for Technology and Disability Studies, Box 357920, Seattle, WA 98195, USA.
Notes	

Reynolds 2002

Methods	Study design: Case -controlled study
Participants	Baseline Characteristics Included criteria: leukemia cases were diagnosed in children under age 5 years between 1988 and 1997. Excluded criteria: Children with down syndrome, twins and triplets. Pretreatment:
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia

	Outcome type: Dichotomous Outcome
Identification	Sponsorship source: National Cancer Institute. Country: United States of America Setting: California Cancer Registry Authors name: Peggy Reynolds, Julie Von Behren, and Eric P. Elkin Institution: California Cancer Registry Email: Preynold@dhs.ca.gov) Address: 1515 Clay Street, 17th Floor, Oakland, CA 94612
Notes	

Robison 1987

Methods	Study design: Case-Controlled study
Participants	Baseline Characteristics ≤4000g >4000g Overall Included criteria: All cases of ALL diagnosed since January 1969 Excluded criteria: Weights <2000g Pretreatment:
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous Outcome
Identification	Sponsorship source: University of Minnesota Computer Center, and the Children's Cancer Research Fund. Country: USA Setting: University of Minnesota and the Mayo Clinic Authors name: Leslie Robison, Mary Codd and Paul Gunderson Institution: University of Minnesota Health Sciences Center Email: Not reported Address: Minneapolis, Minnesota 55455, U.S.A
Notes	

Schz 2007

Methods	Study design: Case-controlled study
Participants	Baseline Characteristics Included criteria: Cases of ALL diagnosed in children <14 years who have lived in West Germany at the age of diagnosis. Excluded criteria: Children with down syndrome
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome
Identification	Sponsorship source: Intramural Research Program of the NIH, National Cancer

	Institute, and by The Danish Cancer Society Country: Germany Setting: German Childhood Cancer Registry (GCCR) at the University of Mainz. Authors name: Joachim Schuz, Michele R. Forman Institution: University of Mainz Email: Joachim@cancer.dk Address: Strandboulevarden 49, 2100 Copenhagen, Denmark.
Notes	

Sprehe 2010

Methods	Study design: Case-controlled study
Participants	Baseline Characteristics Included criteria: all children that were singleton births and aged <5 years, who were residents of Texas, and had gestational age data, as well as diagnosed with a malignancy between 1995 and 2003 Excluded criteria: Birthweight (BW) was missing; if the BW was , 500g or if conditions diagnosed at birth were likely to cause death during infancy. Pretreatment:
Interventions	Intervention Characteristics ≤4000g >4000g
Outcomes	Acute Lymphoblastic Leukemia Outcome type: Dichotomous outcome
Identification	Sponsorship source: National Cancer Institute training grant R25 CA57730 Country: USA Setting: Texas Department of Health Authors name: Michael R. Sprehe, Nadia Barahmani, Yumei Cao, Tao Wang, Michele R. Forman, Melissa Bondy, and M. Fatih Okcu, Institution: Texas Department of Health Email: mfokcu@txccc.org Address: Clinical Care Center, Suite 1510.19, 6621 Fannin, CC 1510.00.
Notes	

Characteristics of excluded studies

Buckley 1994

Reason for exclusion	Wrong study design

Chokkalingam 2012

Reason for exclusion	Wrong outcomes

Cnattingius 1995

Reason for exclusion	Wrong outcomes

Dorak 2007

Reason for exclusion	Wrong outcomes

Glinianaia 2011

Reason for exclusion	Wrong outcomes

Groves 2018

Reason for exclusion	Wrong intervention

Gruhn 2008

Reason for exclusion	Wrong outcomes

Johnson 2008

Reason for exclusion	Wrong outcomes

Kennedy 2015

Reason for exclusion	No full-text

Murray 2002

Reason for exclusion	Wrong intervention

ONeill 2012

Reason for exclusion	Wrong outcomes

Paltiel 2015

Reason for exclusion	Wrong outcomes

Rafieemehr 2019

Reason for exclusion	Wrong intervention

Roman 2013

Reason for exclusion	Wrong intervention

Westergaard 1997

Reason for exclusion	Wrong intervention

Yeazel 1997

Reason for exclusion	Wrong intervention