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

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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 (≤ 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; Wilm 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 (variably defined as weighing more than 3500g, 4000g and 4500g) are at risk of developing ALL has received a lot of attention (Johnson, Soler, Puunala, 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 (≤ 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 (≤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. ≤ 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.

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Figure 1 (Analysis 1.2)

Caption

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

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 | Kofman 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? | Adverse events reported? | Loss-to-follow up reported? | Actual p-value reported? | Sample asked to participate representative of the population? | Sample agreed to participate representative of the population? | Staff participating representative of the patients’ environment? | Attempt to blind participants? | Attempt to blind assessors? | Data dredging results stated clearly? | Analysis adjusted for length of follow up? | Appropriate statistics? | Reliable compliance? | Accurate outcome measures? | Same population? | Participants recruited at the same time? |
|-------------------|-----------------------------------------------|---------------------------|----------------------------|---------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|-------------------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------|-----------------|-----------------|----------------|----------------|
|                   | No                                            | No                        | No                         | No                         | Yes                                                           | No                                                            | No                                                            | Yes                           | No                           | No                                                            | No                                                            | No                            | No                           | No                           | Yes                           |
|                   | No                                            | No                        | No                         | No                         | Yes                                                           | No                                                            | No                                                            | No                            | No                           | No                                                            | Yes                                                            | No                            | Yes                           | No                           | No                            |
|                   | No                                            | No                        | No                         | Yes                        | No                                                            | No                                                            | No                                                            | No                            | No                           | No                                                            | Yes                                                            | No                            | Yes                           | No                           | No                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | No                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | No                                            | No                        | No                         | No                         | No                                                            | No                                                            | No                                                            | No                            | No                           | No                                                            | No                                                            | No                            | No                           | No                           | No                            |
|                   | No                                            | No                        | No                         | Yes                        | No                                                            | No                                                            | No                                                            | No                            | No                           | No                                                            | Yes                                                            | No                            | Yes                           | No                           | No                            |
|                   | No                                            | No                        | Yes                        | No                         | No                                                            | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | No                                            | Yes                       | No                         | Yes                        | Yes                                                           | No                                                            | No                                                            | No                            | No                           | No                                                            | No                                                            | No                            | No                           | No                           | No                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                   | Yes                                           | Yes                       | Yes                        | Yes                        | Yes                                                           | Yes                                                           | Yes                                                           | Yes                           | Yes                           | Yes                                                            | Yes                                                            | Yes                           | Yes                           | Yes                           | Yes                            |
|                          | Randomised? | Adequate allocation concealment? | Adequate adjustment for confounders? | Loss of follow up reported? | Power calculation? | Total score: (sum of all domains) |
|--------------------------|-------------|----------------------------------|--------------------------------------|-----------------------------|--------------------|----------------------------------|
|                          | No          | No                               | Yes                                  | No                          | No                 | 14                               |
|                          | No          | No                               | No                                   | Yes                         | Yes                | 14                               |
|                          | No          | No                               | No                                   | Yes                         | No                 | 14                               |
|                          | No          | No                               | No                                   | No                          | No                 | 14                               |
|                          | No          | No                               | Yes                                  | No                          | No                 | 14                               |
|                          | No          | No                               | No                                   | Yes                         | No                 | 14                               |
|                          | No          | No                               | No                                   | Yes                         | No                 | 14                               |
|                          | No          | No                               | No                                   | Yes                         | No                 | 14                               |

Total score: 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 |
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 |
|------------|-------------|----------------|------------|-------------|-----------|---------------------|-------------|------------|------------|----------------|-------------------|---------------------|---------------------|----------------|----------------|
| N/A        | N/A         | N/A            | N/A        | N/A         | N/A       | N/A                 | N/A         | N/A        | N/A        | N/A            | N/A                | N/A                 | N/A                 | N/A            | N/A            |

NB: Yes = 1, No = 0, Average of all domains of included studies = 13.5
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 syndrome, others who had missing information for birth weight, and others who had missing information for gestational age at birth. |
| 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. |

### 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. |
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 Lynsje 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 |
| Notes | |
| 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 |

| Interventions | Intervention Characteristics |
|---|---|
| ≤4000g | >4000g |

| Pretreatment: |
|---|

| 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: | Divisão de Medicina Experimental, Centro de Pesquisa – Instituto Nacional De Cáncer, Rio de Janeiro, Rua André 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 |
|---|---|
### 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

### Okcu 2002

#### 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 by the 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 |

| 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                  | XiaoOu.Shu@mcmail.vanderbilt.edu |

### Methods

**Podvin 2006**

| Study design          | Case-controlled study       |
|-----------------------|------------------------------|
| Study grouping        |                              |

| Participants          | Baseline Characteristic      |
|-----------------------|------------------------------|
| Included criteria     | Children, 20 years diagnosed with ALL |
| Excluded criteria     | Infants with Down’s syndrome |

| Interventions         | Intervention Characteristics |
|-----------------------|------------------------------|
| ≤4000g                |                              |
| >4000g                |                              |

| Outcomes              | Acute Lymphoblastic Leukemia Outcome type: Dichotomous Outcome |

### Notes

**Podvin 2006**

**Reynolds 2002**

| Study design          | Case-controlled study       |
|-----------------------|------------------------------|
| Study grouping        |                              |

| 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. |

| Interventions         | Intervention Characteristics |
|-----------------------|------------------------------|
| ≤4000g                |                              |
| >4000g                |                              |

| Outcomes              | Acute Lymphoblastic Leukemia |

### Notes

**Reynolds 2002**
| Identification | Outcome type: Dichotomous Outcome |
|----------------|----------------------------------|
| 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 | |

**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 | |

**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.

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 ≤4000g 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. Srehie, Nadia Barahmani, Yumei Cao, Tao Wang, Michele R. Forman, Melissa Bondy, and M. Fatih Okcu,  
Institution: Texas Department of Health  
Email: mfokcu@txcc.org  
Address: Clinical Care Center, Suite 1510.19, 6621 Fannin, CC 1510.00. |

Notes

| Characteristics of excluded studies |
|------------------------------------|
| Buckley 1994 | Wrong study design |
| Chokkalingam 2012 | Wrong outcomes |
| Cnattingius 1995 | Wrong outcomes |
| Dorak 2007 | Wrong outcomes |
| Glinianaia 2011 | Wrong outcomes |

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| Study            | Reason for exclusion |
|------------------|----------------------|
| Groves 2018      | Wrong intervention   |
| Gruhn 2008       | Wrong outcomes       |
| Johnson 2008     | Wrong outcomes       |
| Kennedy 2015     | No full-text         |
| Murray 2002      | Wrong intervention   |
| O’Neill 2012     | Wrong outcomes       |
| Paltiel 2015     | Wrong outcomes       |
| Rafieemehr 2019  | Wrong intervention   |
| Roman 2013       | Wrong intervention   |
| Westergaard 1997 | Wrong intervention   |
| Yeazel 1997      | Wrong intervention   |