



## META-ANALYSIS

### Birth Weight as a Risk Factor for Childhood Leukemia: A Meta-Analysis of 18 Epidemiologic Studies

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Evidence has emerged that childhood leukemia is initiated in utero. High birth weight is one of the few birth-related factors that has been associated with childhood leukemia, albeit not consistently. The authors conducted a meta-analysis of studies of the association between birth weight and childhood leukemia risk. Study-specific odds ratios for leukemia were calculated, using a cutoff at 4,000 g of birth weight. The authors also evaluated whether the association between birth weight and leukemia followed a log-linear dose-response-like pattern. They calculated summary estimates using weighted averages of study-specific odds ratios from dichotomous and trend analyses. Eighteen studies (published between 1962 and 2002) were included, encompassing 10,282 children with leukemia. Children weighing 4,000 g or more at birth were at higher risk of acute lymphoblastic leukemia than children weighing less (odds ratio (OR) = 1.26, 95% confidence interval (CI): 1.17, 1.37). Furthermore, data were consistent with a dose-response-like effect (OR = 1.14/1,000-g birth weight increase, 95% CI: 1.08, 1.20). Studies of acute myeloid leukemia indicated a similar increase in risk for children weighing 4,000 g or more at birth (OR = 1.27, 95% CI: 0.73, 2.20) and a dose-response-like effect (OR = 1.29/1,000 g, 95% CI: 0.80, 2.06), but results varied across studies. Our findings support a relation between birth weight and childhood acute lymphoblastic leukemia risk and emphasize the need for additional studies of the biologic mechanisms underlying this association.

birth weight; child; leukemia, lymphocytic, acute; meta-analysis; risk factors

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; IGF-I, insulin-like growth factor I; OR, odds ratio.

In recent years, compelling evidence has emerged that the development of childhood leukemia is initiated in utero. In particular, it is now apparent that cells with certain chromosomal translocations specific to leukemic cells, such as t(12;21), t(4;11), or t(8;21), are often already present at birth in children who later develop leukemia (1–4). This insight into the natural history and chronology of infant and childhood leukemia emphasizes the significance of prenatal exposures to the leukemogenic process. So far,

however, few prenatal risk factors for leukemia have been identified (5, 6).

Birth weight is determined by a range of genetic traits and exposures occurring in the intrauterine environment (7). Of interest, some epidemiologic studies have reported high birth weight as a leukemia risk factor (8–21). However, other studies have not demonstrated this relation (22–27). Importantly, some studies were too small to detect an association, and it is uncertain whether the different findings across

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studies were due to differences in study population or design. In addition, it is unclear whether the possible association with birth weight follows a dose-response-like pattern as demonstrated by some investigators (11, 16–18, 21) or if, instead, increased leukemia risk is restricted to children with extremely high birth weights. Despite the extent of the literature, a recent review of this question concluded that the association between high birth weight and childhood leukemia was uncertain (28).

We conducted a meta-analysis of epidemiologic studies of the association between birth weight and childhood leukemia. We sought to assess the consistency of the association across studies and to determine whether the association could be discerned separately for the two leukemia subtypes, acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). We also tested whether the association between birth weight and leukemia risk followed a dose-response-like pattern.

## MATERIALS AND METHODS

### Study base

We identified epidemiologic studies of the association between birth weight and childhood leukemia, listed in Medline or Embase before May 1, 2002. Specifically, we performed a literature search using the index terms *child, leukemia, cancer, epidemiology, risk factor, case control, cohort, and birth weight*, in various combinations. To be eligible for inclusion, published studies had to present information on the number of individuals (both cases and controls) in different birth weight strata in addition to corresponding measures of relative risk (e.g., unadjusted or adjusted odds ratios) for leukemia (see “Statistical analyses”).

From a review of abstracts identified in the database search, 53 articles were selected for a full review. The reference lists of the articles were examined, resulting in the additional identification of one article published before 1966 (29) and one book chapter (30). We initially excluded 20 of the total of 55 studies: eight studies did not present any information on birth weight and leukemia risk (31–38), two studies concerned only twins (39, 40), one study used siblings as the control group (41), and nine studies did not present data on leukemia cases separately from other malignancies (42–50). Of the remaining 35 studies, 13 studies were excluded because they did not present data on the number of cases and controls in appropriate birth weight strata (see “Statistical analyses”) (13, 14, 17, 20, 23, 29, 30, 51–56), and four studies overlapped with other included studies (24, 57–59) (appendix table 1). Thus, the present meta-analysis includes 18 unique studies (appendix table 2): 15 case-control studies, one cohort study, and two “case referent” studies, which compared birth weights in cases with external birth weight distribution data.

Data were independently extracted by three authors (L. L. H., T. W., H. H.), using standardized data extraction forms. Discrepancies in the extracted results (which were generally minor) were resolved through discussion among the authors. For each study, extracted information included the number of cases and controls, in as detailed birth weight strata as

possible, together with corresponding unadjusted and/or adjusted odds ratios and 95 percent confidence intervals. The outcomes considered were ALL, AML, and leukemia combined (for studies that did not differentiate among leukemia types). In addition, we extracted information on study matching factors and factors for which statistical adjustment was performed.

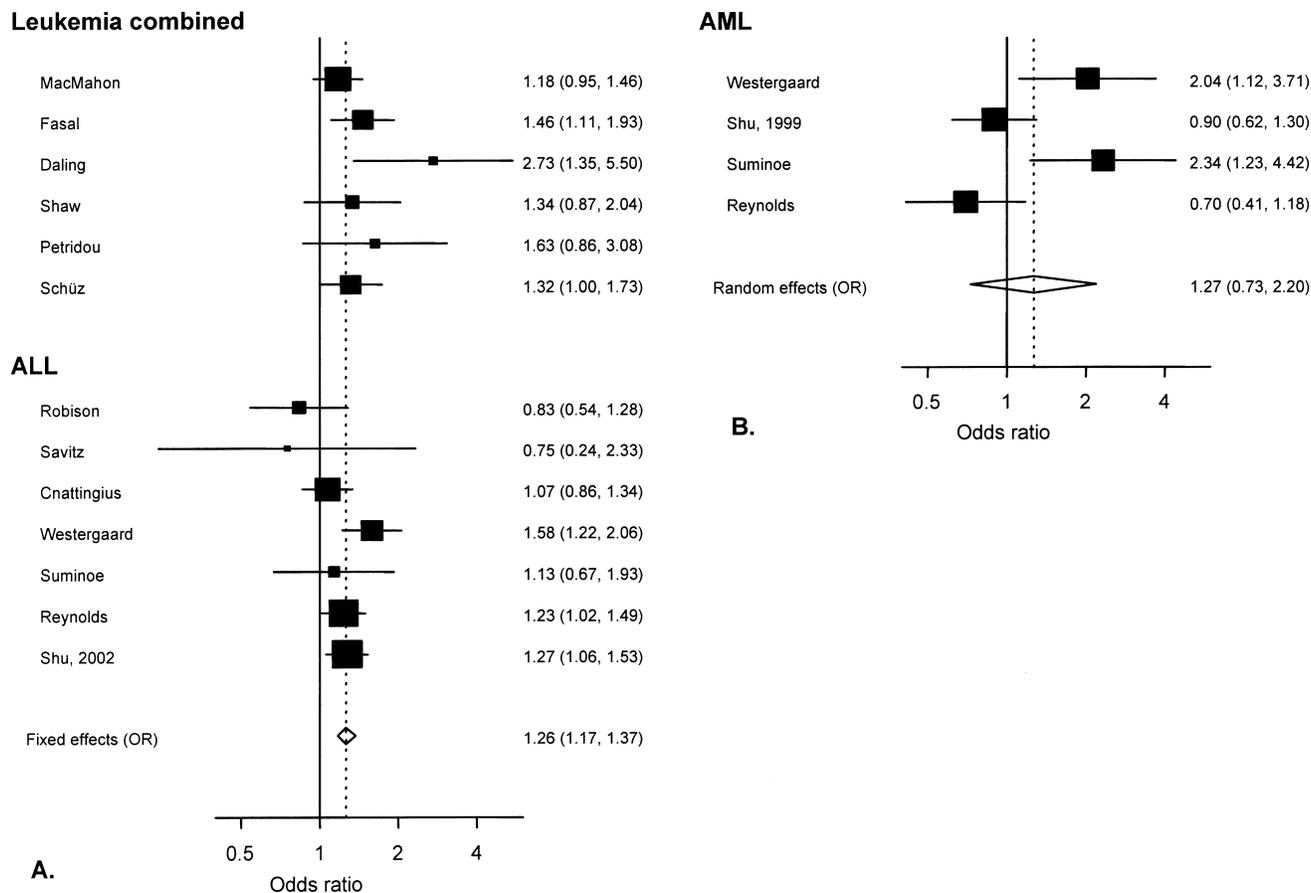
### Statistical analysis

**Dichotomous comparisons.** To obtain a uniform measure of association across studies, we used a birth weight cutoff of 4,000 g and extracted data from each study, when available, on the number of cases (separately for ALL, AML, and leukemia combined) and controls with birth weights above or below this value. We then calculated corresponding crude odds ratios. One study provided mean birth weights for cases and controls along with standard deviations (22). Here we estimated the number of cases and controls above and below 4,000 g by assuming that the birth weights were normally distributed. We also used data provided by the case referent studies to calculate an odds ratio for leukemia associated with high birth weight (10, 60). For instance, Daling et al. (10) reported that 11 leukemia cases had a birth weight over 4,000 g versus 4.9 cases expected. Because Daling et al. also reported that 13 percent of children in the general population had birth weights over 4,000 g, we calculated the total number of leukemia cases studied as  $4.9/0.13 = 37$ . Thus, the odds ratio for leukemia given birth weight over 4,000 g was  $[11/(37 - 11)]/(0.13/0.87) = 2.76$ . The variance of the natural logarithm of this odds ratio was estimated as  $1/11 + 1/26 = 0.13$ .

The majority of the included studies were individually matched case-control studies. To test the effect of ignoring the matching status in calculating birth weight stratum-specific odds ratios, we compared our calculated crude odds ratios for each birth weight stratum with the unadjusted and adjusted odds ratios presented in the published papers.

**Trend analysis for unadjusted and adjusted odds ratios.** For studies that provided data for three or more birth weight strata, we evaluated whether the association between birth weight and risk of leukemia (ALL, AML, or leukemia combined) followed a dose-response-like pattern, that is, could be described adequately by a log-linear model. Specifically, for each study, we calculated birth weight stratum-specific crude odds ratios and confidence intervals as described by Greenland and Longnecker (61). Of relevance for meta-analysis, the method of Greenland and Longnecker also provides a regression coefficient (slope) and corresponding confidence interval quantifying the change in risk (on the logit scale) for each unit of increase in birth weight. Equivalently, exponentiation of the regression coefficient provides an odds ratio for change in risk for each unit of increase in birth weight. Examination of the plots of the stratum-specific odds ratios and the fitted log-linear trend allowed a visual assessment of model adequacy. Similarly, for the single cohort study (16), we examined the log-linear trend in rate ratios across birth weight strata (61).

**Meta-analysis statistics.** Because approximately 80 percent of leukemia cases arising in childhood are ALL (62),



**FIGURE 1.** Odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) for leukemia in children with a birth weight equal to or above 4,000 g compared with those in children with a birth weight below 4,000 g. The studies are grouped by outcome and ordered by publication year. For each study, the size of the boxes is proportional in area to the weight that the study has in calculating the summary effect estimates, which are also displayed. In A, the fixed effects odds ratios for 13 studies with leukemia combined or acute lymphoblastic leukemia (ALL) as outcome are displayed. The  $Q$  statistic was 16.6, indicating no heterogeneity ( $p = 0.17$ ). The random effects odds ratio of 1.25 (95% CI: 1.14, 1.38) was similar to the fixed effects odds ratio. In B, the random effects odds ratios for four studies of acute myeloid leukemia (AML) are demonstrated. There was heterogeneity among the studies ( $Q$  statistic = 13.4,  $p = 0.004$ ).

study-specific odds ratios for ALL and leukemia combined studies were considered together. Thus, for each outcome (ALL/leukemia combined, AML), we had two measures of association with birth weight, namely, dichotomous odds ratios calculated for a cutoff of 4,000 g and a regression coefficient from the trend analysis. As a summary estimate, we then derived a fixed effects odds ratio, which is the inverse-variance weighted average of the study-specific estimates, for either the dichotomous odds ratios (averaged on the log scale) or the regression coefficients (63). The fixed effects summary estimate represents an estimate of the *common value across studies* of the effect of birth weight on leukemia risk (64).

For each fixed effects odds ratio, we calculated a  $Q$  statistic, which quantifies the degree of variability (heterogeneity) in the measures across studies (65, 66). Under the null hypothesis of no difference in effect across studies, the  $Q$  statistic is  $\chi^2$  distributed with degrees of freedom equal to the number of studies minus one. When the  $p$  value of the  $Q$  statistic was less than 0.10, we considered the studies to

exhibit heterogeneity in their effect estimates (63, 64, 66), and in those instances we do not report the fixed effects odds ratio but only the random effects odds ratio. The random effects odds ratio is a weighted average of study-specific odds ratios that takes account of heterogeneity and can be interpreted as the *average across studies* of the effects of birth weight on leukemia risk (63, 64, 66).

**Study characteristics and quality.** Each study was categorized according to characteristics of study design, subjects, and methods. Specifically, we determined whether each study examined leukemia incidence or mortality, whether potential cases had at least 80 percent participation rate, whether controls were known to be alive at the time of index case diagnosis, and how birth weight was ascertained (from interview or registry data). We then examined whether measures of association between birth weight and leukemia differed between studies with different characteristics (67).

**Publication bias.** Using the funnel plot method, we investigated whether there was publication bias among the included studies (68).

## RESULTS

### Description of studies

The 18 studies included in the meta-analysis were published between 1962 and 2002, and they included 10,282 children with leukemia (5,281 with ALL, 963 with AML, and 4,038 with leukemia combined). With two exceptions, the age span of cases was similar across studies (roughly 0–14 years). Daling et al. (10) included only children aged 0–1 year, and Roman et al. (25) had an upper age limit of 29 years. However, in the latter study, the vast majority of ALL cases were diagnosed before the age of 15 years (25) (appendix table 2).

### Dichotomous comparisons

Altogether, 14 studies met the inclusion criteria for the dichotomous comparisons, that is, presented information on the number of cases and controls with birth weight above and below 4,000 g. Figure 1 presents the study-specific crude odds ratio estimates for the effect of high birth weight ( $\geq 4,000$  g vs.  $< 4,000$  g) on the risk of ALL, AML, and leukemia combined. For ALL, the fixed effects odds ratio was 1.22 (95 percent confidence interval (CI): 1.10, 1.35; based on seven studies), and for leukemia combined it was 1.34 (95 percent CI: 1.17, 1.53; six studies). Together, studies of ALL and leukemia combined yielded a fixed effects odds ratio of 1.26 (95 percent CI: 1.17, 1.37; figure 1). There was little heterogeneity in these odds ratios across studies ( $Q$  statistic  $p = 0.17$ ). For comparison, four studies of ALL and leukemia combined presented data at a birth weight cutoff of 4,500 g (12, 15, 16, 22). Together, these studies yielded a fixed effects odds ratio of 1.43 (95 percent CI: 0.97, 2.10;  $Q$  statistic  $p = 0.68$ ) for the effect of birth weight of  $\geq 4,500$  g versus  $< 4,500$  g. Finally, we made a dichotomous comparison of low birth weight children ( $< 3,000$  g) with children of average birth weight (3,000–3,499 g). Six studies of ALL and leukemia combined (9, 15, 16, 18, 21, 22) could be used in this analysis, yielding a fixed effects summary odds ratio of 0.94 (95 percent CI: 0.84, 1.06;  $Q$  statistic  $p = 0.81$ ) for the effect of birth weight of  $< 3,000$  g compared with 3,000–3,499 g.

Only four studies provided sufficient information on AML and birth weight to allow comparison of children with birth weights above or below 4,000 g. Odds ratios appeared to vary across studies (figure 1), and, correspondingly, heterogeneity in these odds ratios was significant ( $p = 0.004$ ). The random effects odds ratio was 1.27 (95 percent CI: 0.73, 2.20).

The estimated crude birth weight stratum-specific odds ratios did not differ materially from the unadjusted and adjusted odds ratios presented in the individual papers (data not shown).

### Trend analysis

Fifteen studies were eligible for the trend analyses, that is, presented data on the number of cases and controls in three or more birth weight strata. Figure 2 shows birth weight

stratum-specific crude odds ratios for ALL or leukemia combined, from the eight largest studies providing such data, along with a fitted log-linear trend. In all cases but two (11, 19), the linear model appeared to fit the odds ratios well. The study-specific adjusted odds ratios, when provided, were similar to these crude odds ratios (data not shown).

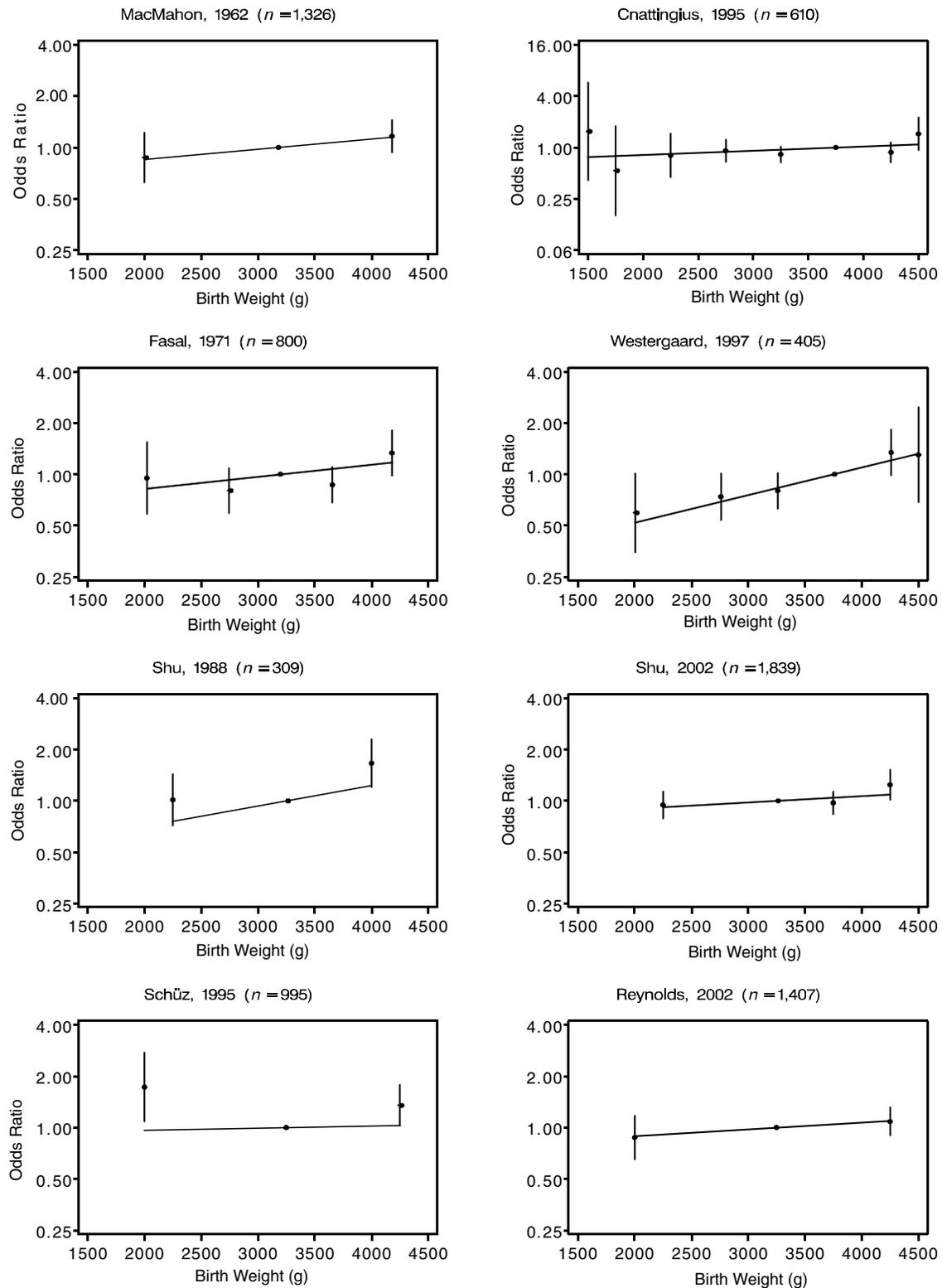
Figure 3 presents the summary estimate for the log-linear effect of birth weight on ALL risk based on data from seven studies with combined leukemia as the outcome and eight studies with ALL as the outcome. There was a statistically significant log-linear relation between birth weight and risk of ALL (fixed effects odds ratio (OR) = 1.14/1,000-g increase in birth weight, 95 percent CI: 1.08, 1.20; figure 3). There was little heterogeneity across studies ( $p = 0.20$ ). One cohort study by Westergaard et al. (16) appeared to find a larger effect than the other studies (OR = 1.45/1,000 g). Excluding this study from the analysis reduced the overall heterogeneity ( $p = 0.66$ ) but did not materially change the fixed effects odds ratio (OR = 1.12, 95 percent CI: 1.06, 1.18). Separately, the fixed effects odds ratios for ALL and leukemia combined were similar (OR = 1.12/1,000 g, 95 percent CI: 1.05, 1.19 and OR = 1.18, 95 percent CI: 1.08, 1.28, respectively).

For AML, there was heterogeneity among the four studies in their estimates of the log-linear effect of birth weight ( $p = 0.002$ ) (16, 25, 27, 69). The random effects odds ratio was 1.29/1,000 g (95 percent CI: 0.80, 2.06).

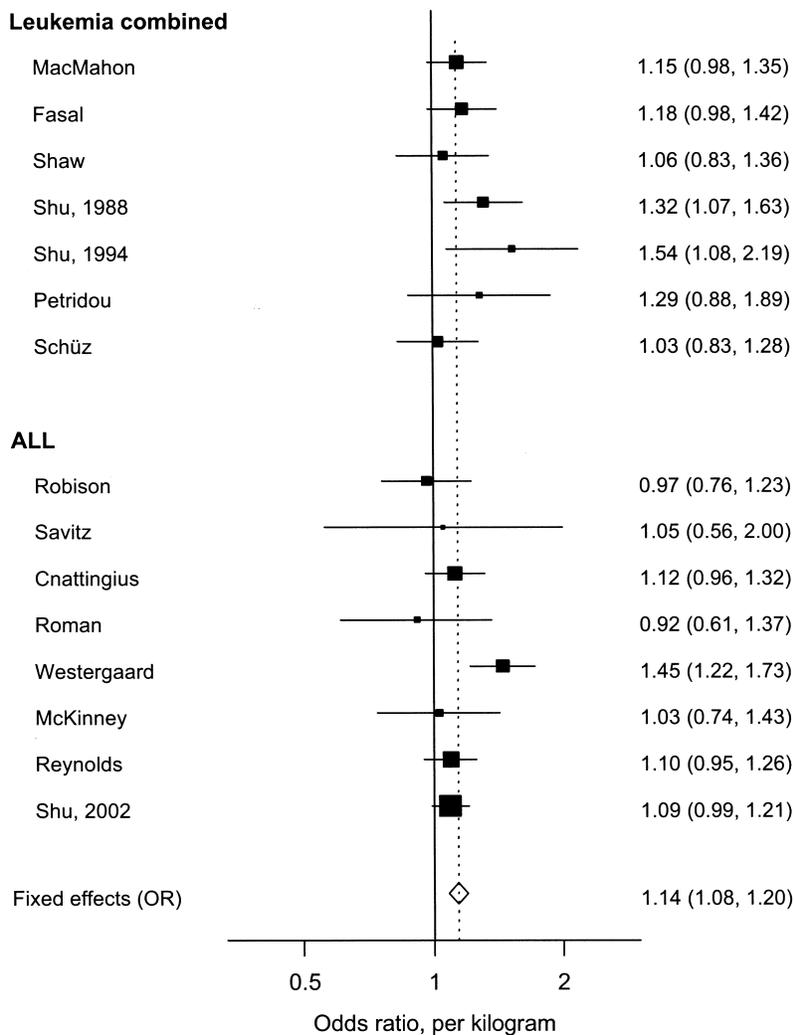
### Study characteristics and quality

Table 1 presents details on the design, subjects, and methods for the 18 individual studies. Stratified analyses according to different study characteristics were based on the study-specific trend estimates for ALL and leukemia combined (figure 3). These stratified analyses yielded almost uniform summary odds ratio estimates. Specifically, these odds ratios did not differ between studies with a participation rate above 80 percent (fixed effects OR = 1.16, 95 percent CI: 1.09, 1.24; six studies) and studies with a case participation rate below 80 percent or “not available” (fixed effects OR = 1.10, 95 percent CI: 1.01, 1.20; nine studies), or between studies where controls were known to be alive at the time of case diagnosis (fixed effects OR = 1.16, 95 percent CI: 1.10, 1.23; 11 studies) and studies where this was not the case (fixed effects OR = 1.07, 95 percent CI: 0.95, 1.20; four studies), or between studies with birth weight ascertained from interview (fixed effects OR = 1.14, 95 percent CI: 1.05, 1.23; six studies) and studies from registry data (fixed effects OR = 1.14, 95 percent CI: 1.07, 1.22; nine studies).

Two studies examined leukemia mortality (fixed effects OR = 1.16, 95 percent CI: 1.03, 1.31). The fixed effects odds ratio from the 13 studies that examined leukemia incidence was 1.14 (95 percent CI: 1.08, 1.20;  $p = 0.12$  for heterogeneity). Heterogeneity was reduced substantially by leaving out the findings of Westergaard et al. (16) from the incidence studies, although this did not markedly change the summary estimate (fixed effects OR = 1.11, 95 percent CI: 1.04, 1.17;  $p = 0.57$  for heterogeneity).



**FIGURE 2.** Birth weight stratum-specific odds ratios (with corresponding 95% confidence intervals) for the eight largest studies (according to number of leukemia cases) included in the meta-analysis. The left column presents studies of leukemia combined, and the right column presents studies of acute lymphoblastic leukemia. Above each panel are presented the author name, publication year, and number of cases in the study. Within each panel, a log-linear regression line through the odds ratios is displayed.



**FIGURE 3.** Study-specific crude odds ratios (ORs) for leukemia, per 1,000-g increase in birth weight for acute lymphoblastic leukemia (ALL) and leukemia combined, derived from the log-linear models (see Materials and Methods). For each study, the size of the boxes is proportional in area to the weight that the study has in calculating the fixed effects odds ratio, which is also shown. The  $Q$  statistic was 18.0, indicating the absence of heterogeneity ( $p = 0.21$ ). For comparison, the random effects odds ratio was 1.14 (95% confidence interval: 1.08, 1.22).

### Publication bias

We did not find any evidence of publication bias (data not shown).

### DISCUSSION

We analyzed 18 epidemiologic studies of the association between birth weight and leukemia, including information on more than 10,000 children with leukemia. The analyses demonstrated a significantly increased risk of ALL in children with high birth weights ( $\geq 4,000$  g vs.  $< 4,000$  g), corresponding to an odds ratio of 1.26 (95 percent CI: 1.17, 1.37). Importantly, most studies, although not all, demonstrated a clear dose-response relation between birth weight and leukemia risk, with ALL risk increasing approximately 14

percent per 1,000-g increase in birth weight (figures 2 and 3). Similarly, although data were limited, ALL risk appeared to increase steadily with birth weight when we conducted additional dichotomous analyses using other birth weight categories ( $< 3,000$  g vs. 3,000–3,499 g, and  $\geq 4,500$  g vs.  $< 4,500$  g). The association between birth weight and leukemia risk was observed consistently in studies conducted over a period of more than 40 years.

The evidence of an association with birth weight was less clear for AML. Only four AML studies, with data on 963 children, were available for analysis. Compared with ALL, the results from both the dichotomous and trend analyses indicated a similar, or even slightly stronger, association with birth weight, but none of the summary odds ratios reached statistical significance. The results of the AML

TABLE 1. Study characteristics and quality

Authors (reference no.)	Leukemia outcome	Source of cases and controls	Cases included in the birth weight analysis (%)	Birth weight source	Controls alive at the time of case diagnosis	Matching factors	Adjusting factors
MacMahon et al. (8)	Mortality	Cancer registry/population controls	NA*	Registry	No	AB,* BP*	
Fasal et al. (9)	Mortality	Cancer registry/population controls	NA	Registry	Yes	S,* AB, BP, BO,* R*	
Daling et al. (10)	Mortality	Cancer registry/population statistics	NA	Registry	NR*	NR	S, CP*
Shaw et al. (22)	Incidence	Cancer registry/population controls	78	Registry	No	S, AB, BP	
Robison et al. (12)	Incidence	Hospital records/population controls	42	Registry	No	AB, BP	
Shu et al. (11)	Incidence	Cancer registry/community controls	93	Interview	Yes	S, AD*	BO, BP†
Savitz and Ananth (80)	Incidence	Cancer registry/community controls	66	Interview	Yes	S, G*	
Shu et al. (79)	Incidence	Cancer registry/population controls	NA	Interview	Yes	S, AD, G	
Cnattingius et al. (15)	Incidence	Cancer registry/population controls	97	Registry	Yes	S, AB	GA*
Roman et al. (25)	Incidence	Cancer registries/population controls	NA	Registry	No	S, AB, BP	
Petridou et al. (18)	Incidence	Hospital records/hospital controls	100	Interview	Yes	S, AD, G	
Westergaard et al. (16)	Incidence	Cancer registry/population cohort	ALL* = 98 AML* = 94	Registry	NR	NR	S, AB, MA,* BO, CP
McKinney et al. (26)	Incidence	Cancer registry/population controls	NA	Registry and interview	Yes	S, AB, G	
Shu et al. (69)	Incidence	Hospital records/community controls	AML = 72	Interview	Yes	AD, G, R	
Schüz et al. (19)	Incidence	Cancer registry/population controls	NA	Interview	Yes	S, AD, G	SES*
Suminoe et al. (60)	Incidence	Cancer registry/population statistics	ALL = 95 AML = 94	Registry	NR	NR	S
Shu et al. (21)	Incidence	Hospital records/community controls	ALL = 88	Interview	Yes	AD, G, R	SES, MA, R
Reynolds et al. (27)	Incidence	Cancer registry/population controls	ALL = 88 AML = 88	Registry	Yes	AB, S	GA

\* NA, not available; AB, age at birth; BP, birthplace; S, sex; BO, birth order; R, race; NR, not relevant; CP, calendar period; AD, age at diagnosis; G, geographic location at diagnosis; GA, gestational age; ALL, acute lymphoblastic leukemia; MA, maternal age; AML, acute myeloid leukemia; SES, socioeconomic status.

† X-ray exposure, prenatal and paternal preconception, chloramphenicol and syntomycin usage, mother's age at menarche, and maternal occupational exposure.

investigations were heterogeneous, and, consequently, our analysis did not allow any firm conclusion as to whether AML risk is indeed increased in children of high birth weight. Accordingly, the rest of the discussion will focus exclusively on ALL.

Childhood leukemia, like other cancers, is believed to arise as a consequence of successively acquired genetic aber-

rations (62). Recent studies have shown that cells with genetic aberrations identical to those observed at ALL diagnosis, specifically chromosomal translocations t(12;21) and t(4;11), are present at birth (1–3), indicating that the first step(s) in leukemogenesis can occur before birth. Ultimately, this process leads to the uncontrolled proliferation and accumulation of a single clone of immature lymphoblasts (62). It

remains to be explained how the association between birth weight and leukemia risk might fit into this process. High birth weight may result from high levels of growth factors in utero, and these growth factors might increase the risk of ALL by inducing proliferative stress on the bone marrow (70, 71). In this regard, insulin-like growth factor I (IGF-I) is essential for somatic growth, and high birth weight infants tend to display high circulating levels of IGF-I (70). IGF-I plays a role in normal hematopoiesis (72–74). Of interest, IGF-I receptors are also present on leukemic lymphoblasts, and IGF-I can stimulate growth of leukemic cells in vitro (73). Additionally, total bone marrow volume has been found to correlate with the weight of the fetus as well as birth weight (75, 76). Thus, children with high birth weight may merely have a higher absolute number of cells susceptible to random genetic aberrations. These potential mechanisms (proliferative stress or increased bone marrow volume), which are not mutually exclusive, could increase the probability of genetic hits (e.g., t(12;21)) arising before birth or in early postnatal life. Importantly, these hypothesized mechanisms are consistent with the observed log-linear association between birth weight and ALL risk (figure 2).

The link between birth weight and risk might be present for all subtypes of ALL. Alternatively, high birth weight could be associated with specific ALL subtypes if, for example, only certain types of preleukemic cells respond to the relevant growth factors. Certain subtypes of ALL (i.e., infant ALL or B-precursor ALL) can be identified indirectly by using age at diagnosis (6, 62). Some studies have reported that the association between birth weight and leukemia risk is strongest for children below 2 years of age (10, 15, 17), while others have not confirmed this finding (16, 21, 27). We were not able to test this hypothesis, because only four studies included in the present analysis presented data stratified by age and not in identical age strata (12, 15, 16, 27), and only one study had information on subtypes of ALL (21).

The potential influence of bias needs to be considered. Publication bias (i.e., the possibility of important negative studies not being published) is a general problem for meta-analyses (77). However, we did not find evidence of publication bias. Furthermore, the majority of the 13 excluded studies also presented an effect of high birth weight on leukemia risk (odds ratios) in the range of 1.5–2.2 (appendix table 1). Bias within studies, such as recall or selection bias, might also have influenced our results. However, recall bias in interview studies is not considered a major problem in the present investigation, because birth weight information obtained from birth certificates or directly from mothers is comparatively precise (78). Selection bias could have been a problem in studies with low participation among cases and controls and in studies where some controls were not alive at the time of case diagnosis. Reassuringly, we did not find evidence that studies with these features provided systematically discrepant results. Two studies (Westergaard et al. (16) and Cnattingius et al. (15)) could be considered almost free of selection bias, because they used nationwide population-based registry data and required that controls were alive at the time of case diagnosis. The article by Westergaard et al., describing the only cohort study, identified a relatively

strong association between birth weight and ALL risk (corresponding to an OR = 1.45/1,000 g, 95 percent CI: 1.22, 1.73). Cnattingius et al. found a weaker association between birth weight and ALL risk that was consistent with the overall summary estimate, although this study did not achieve significance on its own (OR = 1.12/1,000 g, 95 percent CI: 0.96, 1.32). Finally, we evaluated the impact of potential confounding factors within studies by comparing study-specific unadjusted and adjusted odds ratios, and we found little variation (data not shown). Therefore, we believe it is unlikely that bias can explain the observed association between birth weight and ALL risk.

In summary, data from published studies on ALL were consistent with a dose-response-like association between birth weight and risk, with ALL risk increasing approximately 14 percent per 1,000-g increase in birth weight. These results emphasize the need for studies to clarify the biologic mechanisms underlying the birth weight-leukemia association.

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*Appendix follows*

## APPENDIX

APPENDIX TABLE 1. Excluded studies of birth weight and leukemia

Authors (reference no.)	Publication year	Country	Study type	Comment
<i>Reason for exclusion: insufficient data</i>				
Stowens et al. (29)	1961	Italy	Case-referent	At the 50% percentile in the birth weight distribution, the odds ratio for infant leukemia was 1.1 compared with population statistics.
Iversen (51)	1966	Denmark	Case-referent	There were fewer incident leukemia cases with a birth weight of less than 2,500 g compared with the population statistics.
Salonen (52)	1976	Finland	Case-control	The average birth weight of cases = 3,640 g, and the average birth weight of controls = 3,650 g.
Hirayama (30)	1979	Japan	Case-referent	Children aged 0–2 years with a birth weight above 4,000 g had 69% higher risk of acute leukemia than those with a birth weight below 3,400 g.
Windham et al. (53)	1985	Norway	Cohort	In a cohort of children with a birth weight of 2,500 g or less, the rate ratio of observed leukemia cases = 0.9 (95% CI*: 0.4, 1.8) compared with expected.
Eisenberg and Sorahan (23)	1987	Great Britain	Case-control	Odds ratio = 1.0 of leukemia in girls and odds ratio = 1.2 of leukemia in boys comparing birth weight above 4,000 g with birth weights in the range of 2,800–3,200 g.
Kaye et al. (13)†	1991	United States	Case-control	Odds ratio of ALL* = 1.18 (95% CI: 0.84, 1.67) in children with a birth weight above 4,000 g vs. below 4,000 g.
Fajardo-Gutierrez et al. (54)	1993	Mexico	Case-control	Odds ratio of leukemia = 2.21 (95% CI: 1.04, 4.33) in children with a birth weight above 3,500 g vs. below 3,500 g.
Buckley et al. (14)‡	1994	United States	Case-control	Odds ratio of ALL = 1.6, $p < 0.01$ , in children with a birth weight above 3,600 g vs. below 2,700 g.
Ross et al. (55)	1997	United States	Case-control	Odds ratio of infant ALL = 2.15 (95% CI: 1.17, 5.41) and odds ratio of infant AML* = 2.22 (95% CI: 0.82, 6.05) in children with a birth weight above 4,000 g vs. below 3,000 g.
Yeazel et al. (17)§	1997	United States	Case-control	Odds ratio of ALL = 1.5 (95% CI: 1.1, 1.9) and odds ratio of AML = 1.5 (95% CI: 1.0, 2.4) in children with a birth weight above 4,000 g vs. below 4,000 g.
Smulevich et al. (56)	1999	Russia	Case-control	Odds ratio of leukemia = 2.7 (95% CI: 1.2, 5.9) in children with a birth weight below 2,500 g compared with $\geq 2,500$ – $< 4,000$ g.
Murray et al. (20)	2002	Ireland	Cohort	Rate ratio of leukemia = 1.66 (95% CI: 1.18, 2.33) in children with a birth weight above 3,500 g vs. below 3,500 g.
<i>Reason for exclusion: data overlap with an included study</i>				
Zack et al. (24)	1991	Sweden	Case-control	Subset of Cnattingius et al. (15).
Shu et al. (59)	1995	Shanghai, China	Case-control	Subset of Shu et al. (79).
Petridou et al. (57)	1999	Greece	Case-control	Cases identical with cases in Petridou et al. (18).
Mogren et al. (58)	1999	Sweden	Cohort	Cases overlap with those of Cnattingius et al. (15).
Shu et al. (69)	1999	United States	Case-control	Only ALL cases are excluded from this study, because ALL cases are included in the study by Shu et al. (21).

\* CI, confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

† This study covers completely the study by Robison et al. (12) and includes 3 extra study years.

‡ This study covers completely the study by Yeazel et al. (17) and overlaps with the studies by Shu et al. (21, 69).

§ This study is a subset of the study by Buckley et al. (14).

*Appendix continues*

APPENDIX TABLE 2. Included studies of birth weight and leukemia

Authors (reference no.)	Publication year	Case recruitment period	Country	Study type	Cases (no.)	Controls (no.)	Age range of cases (years)
<i>Combined leukemia</i>							
MacMahon and Newill (8)	1962	1947–1958	United States	Case-control	1,323	1,301	0–11
Fasal et al. (9)	1971	1959–1965	United States	Case-control	800	810	1–9
Daling et al. (10)	1984	1974–1982	United States	Case-referent	37	Referent	0–1
Shaw et al. (22)	1984	1975–1980	United States	Case-control	255	510	0–15
Shu et al. (11)	1988	1974–1986	China	Case-control	309	618	0–14
Shu et al. (79)	1994	1986–1991	China	Case-control	166	166	0–14
Petridou et al. (18)	1997	1993–1994	Greece	Case-control	153	300	0–14
Schüz et al. (19)	1999	1980–1997	Germany	Case-control	995	995	0–15
<i>Acute lymphoblastic leukemia</i>							
Robison et al. (12)	1987	1969–?	United States	Case-control	219	1,744	Children
Savitz and Ananth (80)	1994	1976–1983	United States	Case-control	68	208	0–14
Cnattingius et al. (15)	1995	1973–1989	Sweden	Case-control	610	3,061	0–16
Roman et al. (25)	1997	1962–1992	England	Case-control	113	286	0.25–29
Westergaard et al. (16)	1997	1968–1992	Denmark	Cohort	405	Cohort	0–14
McKinney et al. (26)	1999	1991–1994	Scotland	Case-control	124	236	0.25–14
Suminoe et al. (60)	1999	1985–1994	Japan	Case-referent	496	Referent	0–18
Shu et al. (21)	2002	1989–1993	United States	Case-control	1,839	1,985	0–14
Reynolds et al. (27)	2002	1988–1997	United States	Case-control	1,407	2,811	0–4
<i>Acute myeloid leukemia</i>							
Roman et al. (25)	1997	1962–1992	England	Case-control	25	286	0.25–29
Westergaard et al. (16)	1997	1968–1992	Denmark	Cohort	65	Cohort	0–14
Shu et al. (69)	1999	1989–1993	United States	Case-control	456	538	1–14
Suminoe et al. (60)	1999	1985–1994	Japan	Case-referent	177	Referent	0–18
Reynolds et al. (27)	2002	1988–1997	United States	Case-control	240	480	0–4