Birth Weight and Other Risk Factors for Acute Leukemia in the Jerusalem Perinatal Study Cohort

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Abstract

Objectives: To assess the effect of birth weight of children and their siblings and other perinatal/parental factors on the risk of acute leukemia. Methods: We linked data from the Jerusalem Perinatal Study, a population-based research cohort (n = 88,829) of offspring born 1964 to 1976, with Israel's Cancer Registry. Risk factors for acute leukemia were assessed using univariate and multivariate proportional hazards models. Results: Leukemias developed in 65 individuals [24 acute myeloid leukemias (AML) and 41 acute lymphoblastic leukemias (ALL)]. A positive linear relation was found between gender-adjusted birth weight and all leukemias [hazard ratio (HR) 1.85, 95% confidence interval (95% CI) 1.1-3.0] and AML (HR 2.9, 95% CI 1.3-6.4). The association between birth weight and AML was especially notable among infants (HR 8.14, 95% CI 1.8-38.9 for age 0 to 1 year) but was also observed among subjects ages >14 years at diagnosis. The relation was particularly strong among females (P = 0.001). Other risk factors for AML risk on univariate analysis were maternal origin, socioeconomic status, birth weight of sibling > 3,500 g, and family size. On multivariate analysis, only birth weight retained borderline significance (adjusted HR 2.38 per kg, 95% CI 1.0-5.7). Significant predictors for ALL in both univariate and multivariate analyses were male sex (adjusted HR 1.92, 95% CI 1.0-3.7) and birth weight categories $\geq$ 3,000 g introduced into the model as nonlinear terms. Conclusion: Birth weight is associated with an increased risk of acute leukemia in infants, children, and young adults. Perinatal factors play a role in the development of childhood leukemias, but the patterns of association vary by leukemia type. (Cancer Epidemiol Biomarkers Prev 2004;13(6):1057–64)

Introduction

Despite intensive research, the causes of childhood leukemias remain largely undiscovered (1). Current etiologic research suggests that *in utero* exposures are implicated in the causation of infant leukemia and that childhood leukemias may be explained by a ''two hit model'' (reviewed in ref. 2). The first hit occurs most likely during fetal life (often causing a translocation and production of a fusion gene, e.g., *TEL-AML I*), while the second postnatal event causes proliferation of a leukemic clone (2). Prenatal drug and dietary exposures (3-5) have been proposed as causes for the first hit in some leukemias, while infections or aberrant responses to them as well as environmental factors have been suggested as candidates for the second postnatal event (reviewed in ref. 6).

Perinatal characteristics may serve as markers for biological or environmental factors contributing to the causation of childhood leukemia. Previous studies have investigated chromosomal abnormalities such as Down syndrome (7-11), genetic polymorphisms (12, 13), abdominal radiation during pregnancy (reviewed in ref. 14), birth order (15-20), gender (8, 16, 17, 20, 21), and maternal characteristics such as age (7, 8, 11, 15-18, 22, 23), previous reproductive history (8, 10, 15, 16, 20, 24, 25), social class (17, 22, 23, 26), and occupation (18). Other than Down syndrome and radiation during pregnancy, effects of these reported risk factors have been inconsistent.

The association between birth weight and childhood leukemia has been studied by several investigators and reviewed by Ross et al. (27). Nearly all studies used a case-control design, and most included relatively few cases of acute myeloid leukemia (AML). Only two cohort studies have examined the risk of acute leukemia in relation to birth weight; one included *no* cases of AML (28) and the other showed a positive relation between birth weight and childhood AML (19). In one case-control study (25), the association with birth weight was noted beyond early childhood and increased sibling's birth weight was also associated with AML.

Our objective was to evaluate the association between perinatal factors including birth weight and leukemias in a large cohort of children and young adults followed from birth. We were also interested in examining the birth weight of siblings as a predictor of childhood leukemia.

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Subjects and Methods

Study Population. The Jerusalem Perinatal Study cohort includes all offspring born in 1964 to 1976 to residents of western Jerusalem and the surrounding rural county and their parents. The cohort was originally established to study preeclampsia, but the aims were expanded thereafter to include congenital anomalies, perinatal mortality, and other outcomes. Details of this cohort have been published previously (29, 30). Using active surveillance of obstetric wards, baseline data were recorded at birth regarding birth weight, sociodemographic characteristics of the parents, pregnancy and obstetric complications, and congenital anomalies. Further information derived from surveillance of hospitalizations, attendance at mother-child clinics, and review of death certificates was later added to the database.

Linkage. In 2000, we verified the identity numbers and vital status of all the original members of the Jerusalem Perinatal Study cohort. Of the original 91,459 live-born individuals, 88,829 (97.1%) were traced in the Population Registry through their unique identity numbers. Traced individuals were linked to the Israel Cancer Registry, a population-based register established in 1960, which receives documentation of cancer cases from pathology departments, medical records departments, and death certificates. Cancer notification has been required by law since 1982, but even prior to this law, registration of cancer cases was considered to be high (31). Prior to 1982, over 99% of leukemia cases were histologically/cytologically confirmed. Furthermore, <5% of cancer cases were obtained from death certificate information, indicating a high degree of registration. Periodic surveys are carried out for completeness, the most recent of which took place in 1995 to 1997 and showed overall completeness of 90% to 92% for acute leukemias. It is estimated that for childhood malignancy registration is >95% complete. Only the first cancer site per case was included in the analysis. We included all incident leukemia cases (*International Classification of Diseases, Ninth Revision* codes 2040 to 2089).

Statistical Analysis. We calculated person-time incidence of leukemia for the entire cohort by leukemia subtype, age at diagnosis, and gender. We examined the risk of developing leukemia according to sociodemographic, parental, and perinatal factors recorded in the Jerusalem Perinatal Study database using univariate and multivariate Cox proportional hazards methods (32). Follow-up time was measured in days and continued from birth to June 30, 1999, death, or date of first cancer diagnosis. Data are reported as hazard ratios (HR) with 95% confidence intervals (95% CIs).

We studied the risk of leukemia according to age at diagnosis in three categories: 0 to 4, 5 to 14, and 15+ years. The first category was also subdivided (first year of life and age 1 to 4 years). For this analysis, follow-up time began at the beginning of the age category in question (birth, 1, 5, or 15 years). Cases were censored at the time of first cancer diagnosis, and noncases were censored at the upper limit of the age category or at death, if the latter occurred within the age category. For example, for the first category, children diagnosed between birth and age 0.99 years were included as cases and censored at the date of diagnosis, and noncases were censored either at death if it occurred before age 1 year or at age 0.99 years. For the second category, follow-up began at age 1 year. Cases diagnosed prior to age 4.99 years were censored at date of diagnosis, and noncases were censored at death if it occurred before age 5 or at 4.99 years. The next category began follow-up at 5 years and ended at 14.99 years. For the final category (15+), follow-up time began at age 15 years; cases were censored at date of diagnosis, and noncases were censored at death or on June 30, 1999.

Birth weight was analyzed in 500 g categories and as a continuous variable after adjusting for gender. Other variables analyzed included parental characteristics such as place of birth (Israel vs. abroad); ethnic origin (based on grandfather's continent of birth—western Asia, North Africa, or Europe, the latter group also including the Americas, Southern Africa, and Australia), a factor shown previously to be associated with birth weight in this population (33); age at the time of delivery (by 5-year age categories); socioeconomic status (by father's occupation at the time of birth, coded originally into six categories and recoded to a dichotomy of high and low); and education (0 to 8, 9 to 12, or ≥13 years). Furthermore, we examined perinatal factors or obstetric conditions such as birth order (first or other as recorded in the original Jerusalem Perinatal Study data set); sibship size in the assembled cohort (which included the index case and all siblings born 1964 to 1976) classified as 1 to 2, 3 to 4, or ≥5; gender of the offspring; previous fetal or neonatal loss (none vs. at least one); and presence or absence of obstetric interventions and maternal conditions and complications as noted at the time of delivery for which there were at least five cases of acute leukemia. These included induction of labor, vacuum extraction, Rh− mother, fetal distress or asphyxia, and cord deviation. We investigated the effect of the presence of a sibling with birth weight > 3,500 g on leukemia risk. For children with no siblings, the value for this latter variable was set at 0. This analysis was repeated excluding the population without siblings.

Multivariate models were constructed for the risk of AML and acute lymphoblastic leukemia (ALL). Variables, which were entered into these models, included those factors that were significantly ($P < 0.05$) associated with leukemia risk in univariate models. The significance of each independent variable was evaluated by the likelihood ratio test. Individuals with missing values were not included in the models. All statistical analyses were performed using SPSS version 9 (SPSS, Chicago, IL).

The study protocol was approved by the institutional review boards in Jerusalem and New York.

Results

Of the traced offspring in the cohort, 87,078 (98%) were born to Jewish mothers and 1,751 (2%) to non-Jewish mothers (mainly Arabs). Ninety-eight percent of the mothers were married at the time of the birth. Cancer developed among 541 offspring in the Jerusalem Perinatal Study cohort prior to July 1, 1999. Of these, 340 (63%) developed solid tumors and 201 (37%) developed hematopoietic malignancies including 87 Hodgkin's

disease, 49 non–Hodgkin lymphoma, 41 ALL, and 24 AML. Only four cancers occurred among Arabs, all of which were lymphomas. Thus, the analyses for acute leukemia were restricted to Jewish offspring. One child with AML had Down syndrome (birth weight 2,950 g) and one was born to a mother with gestational diabetes (birth weight 3,250 g).

Univariate Analysis. Table 1 shows the person-time incidence of leukemia for each leukemia subtype and by age at diagnosis and gender. The risk of leukemia in the cohort was 2.6/100,000 person-years.

The association of perinatal factors and parental characteristics with leukemia is shown in Table 2. The risk of ''all leukemias'' related to the factors analyzed showed an intermediate pattern between the pattern of ALL and AML. None of the maternal or obstetric conditions and complications analyzed (see Subjects and Methods section) was associated with leukemia risk. There were insufficient data on gestational age to analyze relations between this variable and leukemia risk.

The risk of AML was considerably lower among offspring of mothers born abroad compared with those of mothers born in Israel. Offspring whose maternal grandfather was born in North Africa were particularly protected compared with those with Israel-born grandfathers. There was no relation noted with maternal age. While those with older fathers appeared to be at somewhat higher risk, the CIs crossed unity and the relation was nonmonotonic. Offspring born of women with high socioeconomic status were at greater risk (>2-fold) for the development of AML ($P \leq 0.04$). When socioeconomic status was analyzed in six categories, no linear trend was noted ($P = 0.08$; data not shown). Higher education among the parents was also associated with an increased risk of this disease, but the findings were not statistically significant. There was no association with birth order, but sibship size in the cohort was associated with an increased risk of AML, particularly offspring from families with three to four siblings in the cohort. Male offspring were at increased risk, but the relation was not significant. We found no association with previous fetal or neonatal loss.

Regarding ALL, the pattern of risk differed from that of AML. There was a 2-fold risk of this disease among male offspring compared with females. Socioeconomic status and parental education appeared to show an opposite relation compared with that seen in AML, but the findings were not significant. Birth order and sibship size, parental age, and previous fetal or neonatal loss were unrelated to the risk of ALL.

Table 1. Incidence rates of all leukemias, ALL, and AML by age at diagnosis and gender in the Jerusalem Perinatal Study cohort

	n Cases	Person-Years	Rates per 100,000	95% CI
Overall				
All leukemias	65	2,487,912	2.61	2.0-3.0
ALL	41	2,487,912	1.65	1.1-2.2
AML	24	2,487,912	0.96	0.6-1.4
By age at diagnosis (y)				
All leukemias				
0-4	22	425,618	5.17	3.0-7.4
5-14	18	848,259	2.12	1.1-3.1
15+	25	1,214,039	2.06	1.2-2.9
ALL				
0-4	12	425,618	2.82	1.2-4.5
5-14	15	848,259	1.77	0.8-2.7
15+	14	1,214,039	1.15	0.5-1.8
AML				
0-4	10	425,618	2.35	0.8-3.9
5-14	3	848,259	0.35	−0.1-0.8
15+	11	1,214,039	0.91	0.3-1.5
Males (n = 44,854)				
All leukemias	44	1,279,956	3.44	2.4-4.5
ALL	28	1,279,956	2.19	1.4-3.0
AML	16	1,279,956	1.25	0.6-1.9
Females (n = 42,112)				
All leukemias	21	1,207,955	1.74	1.0-2.5
ALL	13	1,207,955	1.08	0.5-1.7
AML	8	1,207,955	0.66	0.2-1.2

Relation of Birth Weight to Leukemia Risk. Birth weight was available for 86,604 (>99%) members of the cohort. None of the cases of acute leukemia was missing information regarding birth weight. The lowest birth weight category of ≤2,999 g included 25.0% of the cohort, while the highest category (≥4,000 g) included 6.9% of the cohort. Table 3 shows the risk of AML and ALL according to categories of birth weight. A trend for increased leukemia risk by increasing birth weight was observed for all leukemias combined ($P = 0.002$).

A slight increase in risk of AML comparing offspring with low birth weight (<2,999 g) with those in the modal birth weight category (3,000 to 3,499 g) was observed; thereafter, the risk increased with increasing birth weight. This apparent J-shaped relation was based on only four cases of the disease in the lowest category. Furthermore, a test for a nonlinear (quadratic) term was not significant. Indeed, the test for a linear trend by increasing birth weight was highly significant for AML ($P = 0.009$).

For ALL, offspring born in all birth weight categories above a threshold of 3,000 g showed a similar increased risk. There was no monotonic or linear trend (P for linear trend = 0.06). In further analyses regarding ALL, birth weight was analyzed as a categorical variable with four categories, while, for AML, birth weight was entered into the models as a continuous variable. Mean (SD) birth weight was 3,190 (520) g for girls and 3,310 (550) g for boys ($P < 0.0001$). Further analyses of birth weight were thus adjusted for gender.

There was an almost 3-fold risk of AML with each kilogram increase of gender-adjusted birth weight (HR 2.9, 95% CI 1.3-6.4). We examined whether this linear relationship was modified within various subgroups. Examining this relation by age at diagnosis, we found a positive association in children ages 0 to 4 years (HR 4.0, 95% CI 1.2-13.3) and in young adults ages ≥15 years (HR 2.9, 95% CI 0.9-9.2). The association was particularly strong for infants in the first year of life (HR 8.14, 95% CI 1.8-38.9), while for those ages 1 to 4 years, the relation was much less remarkable (HR 2.3, 95% CI 0.5-10.3). Positive relations between gender-adjusted birth weight and AML were found for both sexes, but for female offspring, the linear association was particularly strong (HR 7.86, 95% CI 2.4-26.2, $P = 0.001$). This apparent

Table 2. Family characteristics, perinatal factors, and relative risk of leukemia (univariate analysis)

Variable	Distribution in Cohort*	All Leukemias (n = 65), HR (95% CI)	AML (n = 24), HR (95% CI)	ALL (n = 41), HR (95% CI)
Mother's place of birth				
Israel	38,597	1.0	1.0	1.0
Abroad	48,365	0.60 (0.4-1.0)	0.47 (0.2-1.1)	0.69 (0.4-1.3)
Maternal origin[c]				
Israel	12,112	1.0	1.0	1.0
Other west Asia	26,155	0.64 (0.3-1.3)	0.39 (0.1-1.2)	0.93 (0.4-2.5)
North Africa	20,056	0.75 (0.4-1.6)	0.26 (0.1-1.0)	1.32 (0.5-3.5)
Europe, etc.	28,639	0.59 (0.3-1.2)	0.49 (0.2-1.3)	0.71 (0.3-1.9)
Mother's age				
≤19	4,317	1.0	1.0	1.0
20-24	27,813	1.85 (0.4-7.8)	0.93 (0.1-7.7)	2.77 (0.4-20.8)
25-29	27,221	1.58 (0.3-6.8)	1.59 (0.2-12.3)	1.57 (0.2-12.3)
30-34	16,650	1.80 (0.4-2.9)	1.03 (0.1-9.3)	2.58 (0.3-20.1)
35+	10,916	0.99 (0.2-5.1)	1.19 (0.1-11.4)	0.79 (0.1-8.7)
Father's age				
<25	12,126	1.0	1.0	1.0
25-29	27,594	0.83 (0.4-1.9)	1.53 (0.3-7.4)	0.62 (0.2-1.6)
30-34	21,812	0.92 (0.4-2.1)	2.46 (0.5-11.4)	0.47 (0.2-1.4)
35+	25,430	1.26 (0.6-2.7)	1.41 (0.3-6.7)	1.23 (0.5-2.9)
Socioeconomic status				
Low	39,634	1.0	1.0	1.0
High	47,328	1.18 (0.7-1.9)	2.5 (1.0-6.4)	0.79 (0.4-1.5)
Mother's education (y)				
0-8	27,178	1.0	1.0	1.0
9-12	31,473	0.95 (0.5-1.7)	1.18 (0.4-3.4)	0.85 (0.4-1.8)
13+	26,804	1.02 (0.6-1.9)	1.74 (0.6-4.8)	0.74 (0.3-1.6)
Father's education (y)				
0-8	20,977	1.0	1.0	1.0
9-12	30,707	1.10 (0.6-2.1)	1.62 (0.4-6.3)	0.96 (0.5-2.0)
13+	33,511	1.09 (0.6-2.1)	2.99 (0.9-10.4)	0.62 (0.3-1.4)
Birth order				
First	25,515	1.0	1.0	1.0
Other	61,300	1.07 (0.6-1.8)	0.99 (0.4-2.4)	1.11 (0.6-2.1)
Sibship size in cohort				
1-2	42,717	1.0	1.0	1.0
3-4	31,220	1.96 (1.2-3.3)	3.15 (1.2-8.2)	1.54 (0.8-3.0)
5+	13,025	1.29 (0.6-2.8)	2.16 (0.6-7.7)	0.98 (0.4-2.7)
Gender of offspring				
Female	42,111	1.0	1.0	1.0
Male	44,851	1.98 (1.2-3.3)	1.89 (0.8-4.4)	2.03 (1.1-3.9)
Previous fetal or neonatal loss[b]				
None	77,784	1.0	1.0	1.0
At least one	4,005	1.07 (0.3-3.4)	1.03 (0.1-7.7)	1.08 (0.3-4.5)

*Those with missing values are not included.
[c]Based on maternal grandfather's place of birth.
[b]5133 cohort members had missing values for this variable including four cases of AML.

interaction between gender and birth weight, when formally tested, was associated with a borderline P value of 0.053.

For ALL, there was no significant interaction between birth weight categories and gender. Furthermore, there was no significant association between birth weight and ALL in infants up to 1 year (HR 2.1, 95% CI 0.3-14.9).

We found a positive association between the presence of any sibling weighing >3,500 g on the risk of all leukemias (HR 1.94, 95% CI 1.2-3.1) and the risk of AML (HR 3.10, 95% CI 1.4-7.1). For ALL, this relation was weaker (HR 1.48, 95% CI 0.8-2.8). Removing offspring without siblings from the analysis did not change these relations.

Multivariate Analysis. We constructed a multivariate model for the risk of AML, which included gender, birth weight (per kg), presence of a sibling weighing > 3,500 g, sibship size in the cohort, maternal origin, and socioeconomic status (Table 4A). Only birth weight yielded borderline significant (P = 0.05) HRs on multivariate analysis. The HR (95% CI) for each kilogram of birth weight controlling for these other variables was 2.37 (1.0-5.7). Adding an interaction term between birth weight and gender did not improve the model. For ALL, the factors, which were predictors on univariate analysis, retained their significance on multivariate analysis (Table 4B) including male gender and birth weight ≥ 3,000 g (analyzed in 500 g categories).

Discussion

While the association of childhood ALL with birth weight is well accepted (27), the association with AML

Table 3. Leukemia incidence rates by birth weight

Leukemia Type	Birth Weight Categories (g)	*n* Cases	Person-Years	Rates per 100,000	HR (95% CI)
All leukemias	≤2,999	7	604,256	1.16	1.0
	3,000-3,499	27	1,056,544	2.56	2.21 (1.0-5.1)
	3,500-3,999	23	642,546	3.58	3.09 (1.3-7.2)
	4,000+	8	174,420	4.59	3.96 (1.4-10.9), *P* for linear trend = 0.002
ALL	≤2,999	3	604,256	0.50	1.0
	3,000-3,499	22	1,056,544	2.08	4.19 (1.3-14.0)
	3,500-3,999	12	642,546	1.87	3.76 (1.1-13.3)
	4,000+	4	174,420	2.29	4.63 (1.0-20.7), *P* for linear trend = 0.06
AML	≤2,999	4	604,256	0.66	1.0
	3,000-3,499	5	1,056,544	0.47	0.72 (0.2-2.7)
	3,500-3,999	11	642,546	1.71	2.59 (0.8-8.1)
	4,000+	4	174,420	2.29	3.46 (0.9-13.8), *P* for linear trend = 0.009

is less established. Our findings are consistent with several case-control studies and one cohort study in which AML was found to be related to high birth weight. Furthermore, in this cohort, having a sibling with high birth weight was significantly associated with the risk of AML, with an order of magnitude similar to the effect of increasing birth weight in the proband, although this relation did not retain its significance in multivariate analysis. Socioeconomic status, maternal ethnic origin, and sibship size were associated with AML in univariate but not multivariate analysis. The higher risk of AML among offspring of native-born Israelis compared with offspring of immigrants might be explained by confounding by socioeconomic status or by local environmental exposures. Genetic differences are less likely because there are few generations of Israeli-born Jews, most having immigrated from Europe, western Asia, or North Africa within the last century. We did not find that other perinatal conditions or events were associated with the risk of AML.

On the other hand, for ALL, birth weight and male gender were associated with an increased risk. The latter is a common finding in epidemiologic studies of ALL but has not been reported in all studies (21). The relationship of ALL with birth weight appeared to show a threshold effect above 3,000 g, although there were very few cases with the disease in the lowest birth weight category. We did not find any relation between obstetric and perinatal conditions such as induction of labor, asphyxia, and vacuum extraction and the risk of ALL, but the power of our study to detect these relations was limited.

Several case-control studies have examined the association of birth weight with leukemia in general without specifying subtype (15, 17, 22, 34, 35). Some studies, which specifically examined AML, used a cutoff for high birth weight of 4,000 g (20, 24, 36). Only one of these (36) reported a positive and statistically significant association with an odds ratio (OR) of 1.5. The findings in the latter study were stronger in early childhood (OR 2.5, 95% CI 1.1-1.5 for children up to age 2 years). In our study as well, the association of increased birth weight with infant AML was particularly strong. One study using a cutoff of 3,500 g found a striking OR of 6.2 (95% CI 1.3-29.8; ref. 30), while a second (18) using the same cutoff found a more modest effect (OR 1.9, 95% CI 1.0-8.3). The number of AML cases included in these studies ranged from 10 to 150 (Table 5). A recent case-control study (11) reported a decreased risk of AML with extremes of birth weight. A relation between low birth weight and risk of leukemia has also been observed. Schuz et al. (24) found an effect on leukemia risk at both extremes of weight. Iverson (34), on the other hand, found low birth weight to be somewhat protective, as our findings in ALL also suggest.

To our knowledge, this is the second cohort study demonstrating a positive association between birth weight and AML. The first was reported by Westergaard et al. (19) on a large Danish cohort of nearly 2 million children followed from birth until age 15 years. They showed a relative increase of AML risk per kilogram increase in birth weight of 2.14. The CI reported in that study (1.19-3.85) overlaps with that in our study, enhancing the generalizability of our results. We found a borderline interaction between gender and birth weight

Table 4. Multivariate models of leukemia risk

Variable	HR	95% CI	*P*
A. AML [Model χ^2 (9_{df}) = 25.8, *P* = 0.002]			
Birth weight per kg*	2.37	1.0-5.7	0.05
Sex			
Female	1.0	—	—
Male	1.68	0.7-3.45	0.2
At least one sibling with birth weight > 3,500 g			
No	1.0	—	—
Yes	1.81	0.7-4.7	0.2
Sibship size in the cohort			
1-2	1.0	—	—
3-4	2.69	1.0-7.3	0.06
5+	1.55	0.4-6.1	0.5
Socioeconomic status			
Low	1.0	—	—
High	2.18	0.8-6.0	0.1
Maternal origin			
Israel	1.0	—	—
Other west Asia	0.56	0.2-1.8	0.3
North Africa	0.31	0.1-1.3	0.1
Europe, etc.	0.55	0.2-1.5	0.3
B. ALL [Model χ^2 (4_{df}) = 10.5, *P* = 0.03]			
Birth weight categories (g)			
<3,000	1.0	—	—
3,000-3,499	4.04	1.2-13.5	0.02
3,500-3,999	3.44	1.0-12.2	0.06
4,000+	4.06	0.9-18.2	0.07
Sex			
Female	1.0	—	—
Male	1.92	1.0-3.7	0.05

*Birth weight entered into the model as a continuous variable.

Table 5. Review of studies examining the relation between birth weight and AML and all leukemias excluding studies that only examined cases with ALL

Authors (Reference)	Study Type	AML Cases (%)/All Leukemias
MacMahon and Newill (15)	Death certificate, case-control	140 (8)/1,747
Iverson (34)	Hospital-based cases compared with national data	?/516
Wu et al. (41)	Twin study, comparison of leukemic and nonleukemic twin	10 (20)/50
Fasal et al. (22)	Death certificate, case-control	?/449
Shaw et al. (17)	Case-control	26 (10.2)/255
McKinney et al. (35)	Case-control	23 (13.5)/171
Shu et al. (18)	Case-control	94 (30.4)/309
Zack et al. (8)	Case-control	36 (11)/411
Cnattingius et al. (7)	Nested case-control	98 (100)
Ross et al. (20)	Case-control, infant leukemia only	115 (38)/303
Yeazel et al. (36)	Case-control	232 (13.8)/1,677
Roman et al. (25)	Case-control	15 (10.5)/143
Westergaard et al. (19)	Cohort	114 (13.4)/848
Schuz et al. (24)	Case-control	147 (12.4)/1,184
McKinney et al. (26)	Case-control	20 (13.9)/144
Paltiel, current study	Cohort	24 (36.9)/65

NOTE: Association between birth weight and ALL was reviewed previously by Ross et al. (27).

and its relation with AML [to our knowledge, this has been reported once previously with respect to all leukemias in an early case-control study (22)], which was not evident in the Danish cohort.

Westergaard et al. found, as we did, a relation with sibship size (with an increased risk in sibships ≥ 2 when determined at age 2 or 3 years). In that study as well as in a case-control study (20), birth order was also a significant predictor of AML risk, whereas, in our study, this factor had no effect. Both sibship size and birth order are thought to be proxies for early childhood exposure to infection (23, 37). In our study, high socioeconomic status had a borderline association ($P = 0.05$) with AML, lending, perhaps, indirect support for the proposed infectious etiology of childhood leukemia.

Our study design had several advantages. The existence of the Israel Cancer Registry and the universal access to health care in the country ensure unbiased and complete ascertainment of cases. The Jerusalem Perinatal study database contains information recorded at birth, which was not influenced by recall bias or biases due to other events in the child's or mother's life. Thus, although the number of cases of AML was small, the advantage of our study, compared with most others that have explored this relation, is that it is based on a population-based cohort followed from birth to early adulthood in which data on risk factors and outcome were of high validity. The rates of leukemia overall and by age group were comparable with national rates reported to the Israel Cancer Registry (38). The small number of cases limited the power to analyze multiple factors simultaneously on multivariate analysis. Furthermore, we were restricted to the data on births that occurred within the cohort, which limits the validity of variables such as sibship size (it would be underestimated in our database). In addition, a small portion of the cohort (8%) was born in hospitals where obstetric and maternal conditions were not recorded.

Several mechanisms have been raised to explain the observed relationship between birth weight and acute leukemia. One possibility might be exposure to pelvic radiation in mothers with large babies. Although mothers with high birth weight babies may have been exposed to radiation via pelvimetry, we have no direct evidence that this was the case in our cohort. Another theory has postulated that increased levels of insulin growth factors in high-birth-weight babies reflect abnormal cell growth and turnover (27). Increased levels of *IGF-I*, which are thought to be cancer promoting, have been positively correlated with birth weight (39). Furthermore, the genetically imprinted *IGF-II* gene performs an important function in fetal growth by controlling the supply of maternal nutrients to the fetus (40). Wu et al. (41) have found that loss of the normal (monoallelic paternal) genomic imprinting of *IGF-II* may play a role in leukemogenesis. Thus, cytokine dysregulation or increased levels of growth cytokines may have a common influence on fetal growth and leukemic cell differentiation. Extreme levels of thyroid stimulating hormone, low or high, have also been associated with a decreased risk of childhood acute leukemia (42). Other childhood malignancies such as Wilm's tumors are associated with high birth weight via mechanisms of increased growth factors (27). In our study, the HR (95% CI) associated with increasing birth weight (per kg) for Wilm's tumor ($n = 8$) was 2.5 (0.63-10.08). Thus, one possible explanation for increased leukemia in high-birth-weight babies may be due to a larger population of preleukemic clones in large babies compared with small babies, possibly due to the influence of *IGF-I*.

This study does not provide further data to test this hypothesis. However, the suggestion that the presence of high-birth-weight siblings also confers an increased risk for AML lends strength to the hypothesis that the intrauterine environment and possibly genetic factors contribute to AML risk. Only one previous case-control

Table 5. Review of studies examining the relation between birth weight and AML and all leukemias excluding studies that only examined cases with ALL (Cont'd)

Definition of High Birth Weight	Association with AML	Association with All Leukemias
—	—	Mean for cases 7.37 (501.18) per pound controls 7.32 (501.19) per pound
Low birth weight < 2,500 g	—	3.9% observed, 4.8% expected
—	In 5 of 10 cases, leukemic twin heavier	29 of 42 (70%) leukemic twin heavier
>3,860 g	Not distinguished	Relative risk boys 1.1, girls 2.07
—	—	Mean birth weight cases 3,397 ± 603, controls 3,367 ± 550; $P = 0.61$
—	—	No association
>3,500g	OR 1.9 (1.0-3.3) compared with <3,000 g	OR 1.7 (95% CI 1.2-2.6)
Per 100 g	OR 1.0 (0.9-10)	OR 1.0 (95% CI 1.0-11)
—	No effect	
>4,000 g	OR 2.22 (0.82-6.05)	2.28 (95% CI 1.26-4.13)
>4,000 g	OR 1.5 (1.0-2.4), 0-2 y OR 2.5 (1.1-5.5)	—
>3,500 g	OR 6.2 (1.3-29.8)	1.2 (95% CI 0.8-1.8)
Risk per 1 kg	OR 2.14 (1.19-3.85)	
>4,000 g	Elevated birth weight not significant, data not provided	OR 1.4 (95% CI 1.0-1.8) effect at lower and higher birth weight
≥3,500 g	—	OR 1.12 (95% CI 0.73-1.73)
Risk per 1 kg ≥4,000 g	HR 2.9 (95% CI 1.3-6.4), HR 3.46 (95% CI 0.9-13.8)	HR 1.92 (95% CI 1.2-3.2)

study has shown that a birth weight of >3,500 g in the immediately preceding sibling predicts AML in the proband (OR 7.9, 95% CI 0.9-63.9; ref. 25). Other studies have been limited in their possibility of discovering these effects because they used siblings as controls (43) or have not included data on siblings' birth weight.

A further important finding of our study is that the association observed between AML and high birth weight extends to young adults diagnosed above age 14 years. Roman et al. (25) found an OR (95% CI) for AML of 4.6 (0.5-46.9) for high birth weight based on only three cases in the age group 15+ years. Ferguson et al. (44) reported a relationship between birth weight above the mean and cancer in young adults under age 46 years. A recent Swedish study (45) found an increased risk of cancer at all sites [rate ratio for highest vs. lowest quintile 1.71 (1.14-2.56)] and for nonhormonal cancers (rate ratio 2.07, 95% CI 1.22-3.50) in older cohorts of women (born 1914, 1918, 1922, and 1930). AML was not specifically investigated in that study. Renal cell carcinoma in adult men may be moderately associated with high birth weight (46). Breast cancer in young women is associated with high birth weight (47-49). Thus, given our results, AML may join an enlarging list of cancers in adulthood associated with higher birth weight.

Critical events that might occur between birth and the onset of acute leukemia have yet to be elucidated. The association of birth weight and AML suggests a first hit (or set of hits) *in utero*, occurring in large babies, and a subsequent event later in childhood. One possibility is that the *in utero* genetic hit is more likely to occur in large babies. A second possibility is that larger babies have more stem cells or lymphoid cells at risk for succumbing to a ''second hit'' and development of overt leukemia. The striking relation between birth weight and AML in the first year of life raises the possibility of a specific relationship between the *MLL* gene abnormality [which are found in 65% of infant AML (50)] and birth weight.

On the other hand, although leukemias involving the *MLL* gene are known to have a short latency (50), some leukemias have a latent period spanning several years. For example, a long postnatal latency period has been observed for two children in whom the AML1-ETO fusion protein was present at birth who developed t(8;21)-positive AML at ages 10 and 12 years (51). These cases imply that the second hit may be very remote from the first in some patients with AML, as suggested by the relation between high birth weight and leukemia in young adults in this study.

Evidence from several epidemiologic studies suggests that there is an association between birth weight and selected childhood tumors. The association with AML appears to be stronger than that found with other hematologic malignancies. Moreover, our study suggests that this relation is particularly strong in infants but extends beyond childhood. Further investigations in the basic sciences will be required to elucidate the mechanisms explaining the observed relation. Specifically, studies exploring the risk of leukemia in genotypes conferring high birth weight should be performed.

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