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# Very high birth weight of offspring is associated with an increased risk of leukemia in their mothers: Results of a population-based cohort study

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**Abstract**

Although the association between birth weight and childhood leukemia is well described, the relation between a child's birth weight and parental risk of leukemia is unknown. We linked data from the Jerusalem Perinatal Study to the Israel Cancer Registry to ascertain the incidence of leukemia in mothers and fathers in relation to their offspring's birth weight.

Birth weight ≥4500 g in any of the offspring was associated with a >3-fold risk of leukemia in mothers, but not fathers. Potential mechanisms include shared exposures of high birth weight infants and their mothers, possibly to radiation or growth factors, or genetic pathways leading to both high birth weight and leukemia.


*Keywords:* Birth weight; Leukemia; Macrosomia; Intergenerational effects

## 1. Introduction

Previous studies have shown an association between high birth weight and childhood leukemia [1]. High birth weight has also been identified as a risk factor for some adult cancers [2,3]. Factors related to high birth weight include maternal diabetes, advanced maternal age, maternal height, BMI and weight gain during pregnancy as well as gestational age and the sex of the child [4–6]. Postulated mechanisms for the association of leukemia and birth weight have included exposure to growth factors (e.g. IGF-1) related to somatic growth and leukemogenesis [7], possible common genetic mechanisms or higher cell numbers in larger individuals providing increased opportunity for genetic errors. Accelerated fetal growth, possibly under the influence of IGF-1 has also been associated with childhood acute lymphatic leukemia (ALL) [8]. The relation between leukemia and high birth weight, which is strongest for infant leukemias [9] and in boys [10] may be specific to particular molecular subtypes [11]. This association was reported by our group to extend to late adolescent and early adult leukemia [12]. It is not known to what extent this relation is due to heritable factors, the intra-uterine environment or both. To our knowledge the association between offspring's birth weight, particularly high birth weight, and leukemia risk in the parents has not been addressed. Our aims were to assess this relation in a population-based cohort study with a long follow-up.

## 2. Methods

We utilized data from the Jerusalem Perinatal Study, a population-based research cohort including all births in West Jerusalem between 1964 and 1976 (92,408 offspring, 42,955 mothers and 39,620 fathers). Since all Israeli residents have a unique identification number which is used for Vital Statistics, we were able to verify the identities and obtain updated vital status of 98.5%

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of offspring and 96.9% of the mothers in the Israel Population Registry. Following verification of mothers' and offspring's IDs, we were able to trace most fathers (93.6%) through linkage with the mothers' and offspring's identification numbers. Our study included parents of offspring weighing over 300 g at birth who had verified ID numbers. We excluded parents of twins and infants with congenital malformations, as well as those who were diagnosed with cancer before the cohort inception. Thus, for the purposes of this analysis our study population included 39,336 mothers and 38,031 fathers. The Jerusalem Perinatal Study database contains information on birth characteristics of the newborns, obstetric complications and birth outcomes as well as demographic data on the parents. Details of this cohort have been extensively reported [13].

We assessed the association between offspring's birth weight and risk of leukemia in the parents by examining the hazards associated with having at least one child in the family at the extremes of birth weight, specifically <1500 g or ≥4500 g. There were nine mothers who had at least one child weighing <1500 g as well as another child weighing ≥4500 and 10 fathers with at least one child weighing <1500 g and another weighing ≥4500. Since our focus was on high birth weight, and in order to create mutually exclusive categories these were categorized as having at least one offspring weighing ≥4500 g. We also performed an analysis using birth weight categories of 2500, 2500–4000 and >4000 g. Finally we examined birth weight as a continuous variable, as (birth weight)$^2$ and as (birth weight)$^3$.

Cancer incidence was assessed using linkage with the Israel Cancer Registry updated to 2004. The Cancer Registry has existed since 1960, and cancer reporting has been required by law since 1982, although reporting rates were high (>90%), even prior to this date [14].

We examined leukemias as a whole and then assessed the risk of specific leukemia subtypes according to ICD0 codes (acute lymphoblastic leukaemia – 98353, 98363; chronic myelogenous leukaemia – 98753; acute myeloid leukemia – 98403, 98603, 98613, 98663, 98673, 98713, 98723, 98733, 98743, 98913, 99103; chronic lymphatic leukemia – 98233, 98203; and hairy cell leukemia – 99403).

Analysis of risk of leukemia was performed using univariate Cox models with follow-up time for the parent starting at the date of birth of the last child in the cohort and ending at first leukemia diagnosis, date of death, or 31 December 2004 (see Table 1). In multivariate models we adjusted for the following covariates: We adjusted for age of the parent at the entrance to the cohort (i.e. first birth) as a continuous variable and in categories (see Table 1).

Family size, meaning the number of offspring in the cohort, was categorized as one or two children (reference category), three or four children, or five or more children. Socioeconomic status was coded into six groups by father's occupation and for this analysis re-categorized into low, medium (reference) and high categories. Ethnic origin of the parents was classified according to their religion and country of birth. If Jewish and born in Israel, ethnic origin was classified by the parent's father's place of birth. Final categories for origin were Israel (reference category), Western Asia, North Africa, Western Countries (including North America, Europe, Australia/New Zealand and South Africa) and non-Jewish (mainly Muslim Arab). Educational level was available for over 97% of the parents. This was grouped by categories of maximal years of schooling attained and for the multivariate analysis was dichotomized in the mother to 0–12 years (reference) versus 13+ years (i.e. post-secondary education). In bivariate age-adjusted models we controlled for Caesarian section, gestational and pre-gestational diabetes, as recorded in the original database (never versus ever). Those with missing values were not included in the models.

For a subgroup of mothers interviewed postpartum, data on smoking were available for themselves and their spouses. For the same subgroup, data on mother's prepartum body mass index (BMI = weight in kg/(height in m$^2$)) and height, as well as weight gain during one of their pregnancies were also available. A subgroup analysis was performed in this population. Due to the small number of events in this subgroup, the risk of leukemia was compared in parents with at least one child weighing ≥4500 g, compared to all others.

Analyses were performed separately for mothers and fathers.

All data analysis was performed using SAS Version 9.1 (SAS Institute Inc., Cary, NC, USA.). We report hazard ratios, 95% confidence intervals and *p*-values.

## 3. Results

Fewer than 4% of parents had offspring at the extremes of birth weight. The socio-demographic characteristics of the mothers and fathers with and without offspring at those extremes are shown in Table 1.

Mothers of high birth weight infants (≥4500 g) were more likely to be older and have lower levels of education. As expected, women who gave birth to low birth weight infants were more likely to be smokers. While only about 14% of women without offspring at the birth weight extremes had BMIs of 25 and over, almost 40% of mothers of high birth weight individuals had BMIs over 25. Smoking among fathers was less evidently related to low birth weight. Similarly to the mothers, older fathers were more likely to have offspring weighing ≥4500 g. In neither the mothers nor the fathers were the extremes of birth weight strongly related to ethnic origin or socioeconomic status. Conversely, in both parents, having an extremely small or large infant was more likely to occur in families with five or more offspring. Extremely high birth weight of a child was associated with higher average maternal weight gain in the mother. Furthermore, women who gave birth to babies weighing ≥4500 g were more likely to have been diagnosed with gestational or pre-gestational diabetes.

Among the mothers, 57 developed leukemia (of which 25 were acute myeloid leukemia (AML), 13 were chronic lymphatic leukemia (CLL), and 9 were chronic myeloid leukemia (CML). There were few cases of acute lymphoid leukemia (ALL) ($n = 3$) and hairy cell leukemia (HCL) ($n = 3$). Among the fathers 132 developed leukemia (45 were AML, 47 CLL, 18 were CML, 11 HCL, and seven ALL). Four cases each of leukemias in the mothers and fathers were of an unspecified nature.

Controlling for maternal age, having at least one child weighing 4500 g or more at birth was associated with a 3-fold increase in risk of leukemia compared to not having children at the extremes of birth weight (HR 3.4, 95% confidence interval (CI): 1.06–10.91, $p = 0.04$) (Table 2). This

Table 1
Characteristics of mothers and fathers with and without offspring at extremes of birth weight

| Variable | Mothers | | | Fathers | | |
|---|---|---|---|---|---|---|
| | Mothers with at least one offspring <1500 g $N=576$ (1.5%) | Mothers with at least one offspring ≥4500 g $N=607$ (1.7%) | Mothers without offspring at extremes of birth weight $N=(38153)$ | Fathers with at least one offspring <1500 g $N=490$ (1.2%) | Fathers with at least one offspring ≥4500 g $N=594$ (1.6%) | Fathers without offspring at extremes of birth weight $N=(36947)$ |
| Age at first birth | | | | | | |
| <20 | 66 (11.5%) | 37 (6.1%) | 3,560 (9.3%) | 11 (2.2%) | 4 (0.7%) | 288 (0.8%) |
| 20–24 | 216 (37.5%) | 166 (27.3%) | 15,461 (40.5%) | 118 (24.1%) | 83 (14.0%) | 8,953 (24.2%) |
| 25–29 | 165 (28.6%) | 190 (31.3%) | 10,108 (26.5%) | 167 (34.1%) | 152 (25.6%) | 12,694 (34.4%) |
| 30–34 | 79 (13.7%) | 128 (21.1%) | 5,364 (14.1%) | 102 (20.8%) | 150 (25.2%) | 7,089 (19.2%) |
| 35+ | 50 (8.7%) | 86 (14.2%) | 3,660 (9.6%) | 92 (18.8%) | 205 (34.5%) | 7,923 (21.4%) |
| Mean age at first birth {S.D.} | 26.15 {5.7} | 28.16 {5.8} | 26.31 {5.7} | 29.53 {6.8} | 32.57 {7.3} | 30.13 {6.9} |
| Family size | | | | | | |
| 1–2 | 265 (46%) | 272 (44.8%) | 26,092 (68.4%) | 201 (41%) | 268 (45.1%) | 25,180 (68.2%) |
| 3–4 | 222 (38.5%) | 231 (38.1%) | 9,657 (25.3%) | 208 (42.5%) | 231 (38.9%) | 9,470 (25.6%) |
| 5+ | 89 (15.5%) | 104 (17.1%) | 2,404 (6.3%) | 81 (16.5%) | 95 (16.0%) | 2,297 (6.2%) |
| Origin | | | | | | |
| Asia | 77 (13.4%) | 88 (14.5%) | 5,124 (13.4%) | 75 (15.3%) | 88 (14.8%) | 5,225 (14.1%) |
| Africa | 170 (29.5%) | 118 (19.4%) | 10,656 (27.9%) | 168 (34.3%) | 128 (21.6%) | 10,913 (29.6%) |
| Europe/America | 134 (23.3%) | 196 (32.3%) | 7,959 (20.9%) | 110 (22.5%) | 173 (29.2%) | 7,318 (19.8%) |
| Israel | 185 (32.1%) | 195 (32.1%) | 13,852 (36.3%) | 129 (26.3%) | 195 (32.9%) | 12,941 (35.1%) |
| Not Jewish | 10 (1.7%) | 10 (1.6%) | 562 (1.5%) | 8 (1.6%) | 9 (1.5%) | 521 (1.4%) |
| SES | | | | | | |
| 1–2 | 221 (38.4%) | 248 (40.8%) | 16,313 (42.8%) | 186 (38.9%) | 240 (40.4%) | 15,692 (42.5%) |
| 3–4 | 243 (42.2%) | 225 (37.1%) | 15,025 (39.4%) | 214 (43.7%) | 224 (37.7%) | 14,714 (39.8%) |
| 5–6 | 112 (19.4%) | 134 (22.1%) | 6,815 (17.8%) | 90 (18.4%) | 130 (21.9%) | 6,541 (17.7%) |
| Education | | | | | | |
| Missing | 16 (2.8%) | 16 (2.6%) | 1,208 (3.2%) | 9 (1.8%) | 15 (2.5%) | 1,193 (3.2%) |
| 0–8 years | 194 (33.7%) | 245 (40.4%) | 10,439 (27.4%) | 139 (28.4%) | 165 (27.8%) | 8,478 (22.0%) |
| 9–12 years | 199 (34.5%) | 193 (31.8%) | 14,045 (36.8%) | 180 (36.7%) | 208 (35.0%) | 13,447 (36.4%) |
| 13+ years | 167 (29%) | 153 (25.2%) | 12,461 (32.6%) | 162 (33.1%) | 206 (34.7%) | 13,829 (37.4%) |
| Smoking | | | | | | |
| No | 162 (73.3%) | 148 (90.2%) | 10,619 (82.6%) | 96 (47.5%) | 95 (59%) | 6,977 (55.4%) |
| Yes | 62 (27.7%) | 16 (9.8%) | 2,231 (17.4%) | 106 (52.5%) | 66 (41%) | 5,609 (44.6%) |
| Diabetes (gestational and pregestational) | | | | | | |
| Yes | 17 (3.0%) | 53 (8.7%) | 460 (1.2%) | | | |
| No | 540 (93.7%) | 534 (88%) | 35,978 (94.3%) | | | |
| Missing | 19 (3.3%) | 20 (3.3%) | 1,715 (4.5%) | | | |
| BMI | | | | | | |
| <20 | 50 (25.1%) | 11 (8%) | 3,026 (25.5%) | | | |
| 20–24.99 | 110 (55.3%) | 72 (52.2%) | 7,146 (60.2%) | | | |
| 25+ | 39 (19.6%) | 55 (39.8%) | 1,690 (14.3%) | | | |
| Mean height (cm){S.D.} | 161.2 {6.09} | 164.18 {6.27} | 162.2 {5.95} | | | |
| Caesarian | | | | | | |
| No | 516 (85%) | 483 (15.6%) | 34,958 (91.6%) | | | |
| Yes | 85 (14%) | 90 (83.9%) | 2,546 (6.7%) | | | |
| Missing | 6 (1%) | 3 (0.5%) | 649 (1.7%) | | | |
| Weight gain during pregnancy in kg mean {S.D.} | 10.41 {4.82} | 12.74 {5.95} | 11.23 {4.31} | | | |

result was unchanged after multivariate adjustment for family size, socioeconomic status, origin and education, or adjustment for Caesarian section (HR 3.37, 95% CI: 1.05–10.84) but was somewhat attenuated after adjustment for maternal diabetes (HR 3.12, 95% CI: 0.96–10.20). Having at least one child in the very low birth weight category was not associated with leukemia in mothers. Birth weight assessed as a continuous variable after controlling for maternal age was not associated with an increased risk of leukemia (HR per 1 kg increase in weight 1.30, 95% CI: 0.75–2.27, $p=0.353$), and

Table 2
Bivariate and multivariate models of relative risk of leukemia in mothers and fathers of offspring weighing ≥4500 g or <1500 g

| Model type | Reference category | Exposure categories | HR (95% CI) | *p*-Value |
|---|---|---|---|---|
| Age-adjusted | Mother with no child at extremes of birth weight | Mother with at least one offspring ≥4500 g | 3.38 (1.06–10.85) | 0.04 |
| | | Mother with at least one offspring <1500 g | 1.432 (0.19–10.36) | 0.7 |
| Adjusted for age, family size, SES, origin and education | | Mother with at least one offspring ≥4500 g | 3.40(1.05–11.04) | 0.04 |
| | | Mother with at least one offspring <1500 g | 1.44 (0.20–10.42) | 0.72 |
| Age-adjusted | Father with no child at extremes of birth weight | Father with at least one offspring ≥4500 g | 0.43 (0.06-3.10) | 0.40 |
| | | Father with least one offspring <1500 g | 1.98 (0.63–6.21) | 0.24 |

neither were weight$^2$ or weight$^3$ when included into the models (not shown). Furthermore, when mothers of at least one child weighing 4000 g were compared to those who gave birth to offspring of normal birth weight (2500–4000 g) there was no association with leukemia (HR 1.31, 95% CI: 0.61–2.77).

In the subgroup ($n = 12{,}363$) for whom additional variables were recorded, having at least one child weighing ≥4500 g was associated with a hazard ratio of 13.23 (95% CI: 1.6–104, $p = 0.0145$) compared to not having a child in this birth weight category after controlling for height. In fact increased maternal height was itself inversely related to her risk of leukemia (HR 0.82 (95% CI: 0.74–0.92) per cm of height. Also in this subgroup, the relation between leukemia and having at least one child weighing ≥4500 g was somewhat attenuated after controlling for mother's smoking (HR 6.8, $p = 0.067$). However both models were based on very few cases ($n = 11$). We were unable to construct models of mother's leukemia and BMI and weight gain because of missing data on mothers' weight among the cases with leukemia.

No relation was noted for fathers between overall leukemia risk and birth weight of their offspring. For fathers having at least one offspring weighing ≥4500 g the hazard ratio was 0.43 (95% CI: 0.06–3.10, $p = 0.4$) compared to the reference category. Only one case of leukemia occurred in fathers with offspring at the high extreme of birth weight.

Specific subgroups of leukemia (Table 3) in the mother which were associated with HBW were CLL (HR 11.04, $p = 0.002$) and CML (HR 7.84, $p = 0.05$) but these analyses were severely limited by small numbers.

## 4. Discussion

This study demonstrates that mothers of very high birth weight offspring may be at increased risk of leukemia compared to mothers of infants who are not at the extremes of birth weight. We found no association between infant's birth weight and father's risk of leukemia. The fact that there is a differential effect on parent's risk suggest that the mechanism involved is not simple Mendelian inheritance, and raises the question whether a factor or factors in the intra-uterine environment contribute to both high birth weight and leukemia.

An alternative possibility is that exposures which are a consequence of high birth weight could lead to increased leukemia risk in the mother and her offspring. One such factor could be pelvic irradiation. Mothers of large infants are more likely to be diagnosed with cephalopelvic disproportion (in the past an indication for pelvimetry), potentially exposing them and their offspring to ionizing irradiation. We have no documentation of pelvic irradiation in our data set, although consultation with obstetricians practicing at the time that the cohort was established suggest that radiographic pelvimetry was routinely performed in the 1960s and was more likely to be carried out in infants weighing >4500 g. Though controversial, there does appear to be an increased leukemia risk to the fetus exposed to pelvic or abdominal X-rays during this era [15–17]. In more recent decades ultrasound has largely replaced X-ray pelvimetry, and the association with childhood leukemia is less clear [18]. Although the amount of active bone marrow irradiated during pelvimetry is probably small, risks to the mother are unknown, particularly since it

Table 3
Child's birth weight and relation to specific leukemias in mothers

| | No. of cases | No. with at least one offspring weighing ≥4500 g | Hazard ratio[a] (95%CI) adjusted for mother's age at first birth | Average birth weight of offspring grams (S.D.) |
|---|---|---|---|---|
| All leukemias | 57 | 3 | 3.4 (1.05–10.85) | 3345 (556) |
| AML | 25 | 0 | – | 3360 (505) |
| CLL | 13 | 2 | 11.04 (2.43–50.08) | 3430 (781) |
| CML | 9 | 1 | 7.84 (0.97–63.3) | 3302 (577) |
| NOS | 4 | 0 | – | 3205 (242) |
| ALL | 3 | 0 | – | 3220 (400) |
| HCL | 3 | 0 | – | 3292 (484) |

(–) No cases in HBW category.
[a] Hazard ratio for mothers with at least one offspring >4500 g compared to all others.

is difficult to isolate the effect of pelvic radiography from lifetime accumulated radiation exposure for other diagnostic purposes in adults.

It is possible that the observed relation is actually due to characteristics of the mother which may be reflected in giving birth to a high birth weight infant. BMI has been found to be related to the risk of adult hematopoietic malignancies, including leukemia [19,20]. We were unable to control sufficiently for maternal weight, although McLaughlin et al. [21] have found that high birth weight is related to leukemia in children only when the mother was *not* overweight, suggesting that abnormal fetal growth, perhaps as a result of the intrauterine environment, is responsible for the association between birth weight and leukemia in children. When we adjusted for maternal height, the association between offspring's birth weight and mother's leukemia did not disappear, suggesting that the relationship is not merely due to the mother's own anthropometric characteristics. Neither was it fully explained by maternal diabetes. Macrosomia is related to the risk of Caesarian section [22] and birth trauma [4,5], which expose both mother and infant to medical interventions; however controlling for Caesarian section did not alter our findings.

Other possible explanations for the inter-generational effects we observed could include high levels of both maternal and fetal IGF-1 which serve as growth factors for the fetus in utero [23], but may also be related to leukemogenesis in the offspring [7] and presumably may also exert effects on the mother.

Genomic imprinting has been implicated in leukemias, and parent of origin effects have occasionally been observed [24,25]. Uniparental disomy has been noted as an acquired feature of the disease [26,27]. Our finding of a specific association of leukemia in mothers of infants in the very high birth weight category rather than a continuous relation with increasing birth weight raises questions regarding specific macrosomic phenotypes and their relation to maternal leukemia. Beckwith–Wiedemann, and Prader Willi syndromes are disorders related to excessive growth, uniparental disomy and abnormal imprinting [28,29]; both syndromes have been associated with leukemia in affected individuals [30–34], but have not been reported with maternal cancer. We excluded parents of children with congenital anomalies, which have themselves been reported as risk factors for leukemia [35].

Our study's strengths are its population-based design, near complete follow-up and valid, non-biased ascertainment of cancer. Although hematologic malignancies may be underreported to cancer registries [36] there is no reason to assume that this would occur differentially according to a child's birth weight. The specific leukemias observed in the mothers do not have obvious common risk factors (with a possible exception of ionizing radiation [37]), and given the small numbers, chance associations are possible. Furthermore, mothers who gave birth to high birth weight babies before the cohort inception or after 1976 would be misclassified as having only normal birth weight offspring. Given the rarity of this exposure (only 1.7% of all mothers) this misclassification is unlikely to have substantially biased the results. We await confirmation of our findings in other cohorts that include data which would enable the assessment of inter-generational effects of birth weight. Once confirmed, further work will need to be undertaken to discern why a macrosomic phenotype in at least one offspring is associated with increased leukemia risk in mothers.

## Conflict of interest

None.

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