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Childhood acute lymphoblastic leukaemia and birthweight: Insights from a pooled analysis of case–control data from Germany, the United Kingdom and the United States

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Abstract ***Background:*** Heavy birthweight is one of the few established risk factors for childhood acute lymphoblastic leukaemia (ALL). To provide new insight into this relationship, particularly at the extremes (<1500 and >4500 g), we pooled data from three of the largest childhood cancer case–control studies ever conducted.

Methods: Birthweight and gestational age on 4075 children with ALL and 12,065 controls were collected during the course of three studies conducted in the USA, the UK and Germany in the 1990s. Information was obtained from mothers at interview, and the impact of bias was evaluated using the UK study which accessed birth registrations of participants and non-participants. Odds ratios (OR) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression models.

Results: Children with ALL were, on average, heavier than controls at all gestations, the disparity being driven by a deficit of low-birthweight at all gestations and an excess of high-birthweight at ⩾40 weeks. Overall, a 1.2 (95% CI 1.1–1.3) increase in ALL risk per kg increase in birthweight was observed; the ORs rising from 0.2 (0.1–0.7) at ⩽1500 g through to 1.2 (0.9–1.6) at ⩾4500 g; and 0.8 (0.7–0.9) <10th centile through to 1.3 (1.1–1.4) ⩾90th centile.

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Conclusion: Our findings demonstrate the importance of looking across the full birthweight spectrum when examining associations with disease risk. The new observation of a deficit of very-low-birthweight cases at all gestations has aetiological and study design implications for future work examining not only the in utero origins of ALL, but also other childhood and adult cancers.

1. Introduction

Following the demonstration that the chromosomal translocations that characterise paediatric acute lymphoblastic leukaemia (ALL) can occur in foetal development,[1] evidence that ALL can be initiated in utero has continued to accumulate.[2,3] In this context, the consistent observation that heavy babies (variously defined as weighing more than 3500, 4000 or 4500 g) are at increased risk of developing ALL has received considerable attention.[4–10] With respect to potential aetiological mechanisms, the role of maternal and foetal insulin-like growth factors, which is key to normal growth and development,[11] has been much discussed.[6,8,12–17] However, the underpinning nature of the relationship between ALL and foetal growth across the gestational age spectrum remains unclear; and there is debate about the relative importance of a baby's absolute weight/size at birth versus its rate of foetal growth.[14,16,17]

Although ALL is the commonest paediatric malignancy in the developed world it is nonetheless rare accounting for less than 0.5% of all incident cancers[18]; and so most aetiological studies have adopted a case-control design.[4,8] Live births at the extremes of the birthweight distribution are, however, also rare with under 1% weighing 1500 g or less and only 1–3% weighing 4500 g or more.[5,19] Hence, when presenting information on the relationship between ALL and birthweight most investigators have tended to concentrate on high birthweight, either dichotomising their data (e.g. $<$4000 versus $\geqslant$4000 g) or using relatively conservative cut-points (e.g. $<$2500, 2500–3999 and $\geqslant$4000 g), with only the national Nordic studies publishing information across the full birth weight range.[4,5,8,20] Furthermore, many of the case–control studies on this topic have relied on birth characteristics reported by mothers at interview,[8] with comparatively little consideration given to the potential for selective survival at the extremes of the birthweight distribution and maternal recall bias influencing the findings.

Accordingly, with a view to providing new insight into the association between ALL and birthweight, particularly at the extremes of the distribution, we pooled data from three of the largest childhood cancer case–control studies ever conducted – one from the United States of America (USA), one from the United Kingdom (UK) and one from West Germany.[21–23] In addition, one of the studies (UK) had access to record-based data on those who participated and those who did not which allowed us to explore the influence of selection and recall bias on the observed relationship between birthweight and ALL.

2. Patients and methods

Data were collected during the course of three large case–control studies conducted in the early 1990s, one in the USA, one in the UK and one in West Germany; and salient characteristics of each study are summarised in Table 1. Briefly, all three studies proactively ascertained cases directly from treating centres; matched controls to cases on sex, broad region of residence and age at diagnosis (pseudo-diagnosis) and collected information about birthweight and gestational age during interviews with mothers. Further information about the conduct and ethical approvals of the individual studies are fully described elsewhere,[9,16,21,22,24,25] and summaries can also be found in reports of other pooling projects, most notably those concerning the potential aetiological impact of exposure to electro-magnetic fields.[26–28]

Overall, 4075 ALL cases (USA 1842; UK 1460; Germany 773) were available for the present pooled analysis. The US study (one control per case) was ALL specific, whereas the population-based studies in the UK (two controls per case) and Germany (one control per case) targeted all childhood cancers. With a view to maximising statistical power and the potential for broader representation of the birthweight distribution, all available controls were included in the analyses – yielding 12,065 controls in total (USA 1986; UK 7621; Germany 2458). It is important to note, however, that the findings presented in Section 3 were similar when non-ALL controls were excluded. Children excluded from the present analysis included; 81 with Down's syndrome (71 cases, 10 controls) and 316 that were part of a multiple pregnancy (83 cases 233 controls), with one case and one control with Down's syndrome also being part of a multiple pregnancy. This resulted in a total of 3922 cases and 11,823 controls for analyses, the study specific numbers are shown in brackets in Table 1.

In addition to the pooled analysis, data from the UK study were used to evaluate whether selection and recall biases influenced the findings. Unlike the other two