BMJ open accessible medical research

The 5-minute Apgar score as a predictor of childhood cancer: a population-based cohort study in five million children

Jiong Li,[1] Sven Cnattingus,[2] Mika Gissler,[3] Mogens Vestergaard,[4,5] Carsten Obel,[4,6] Jette Ahrensberg,[5] Jørn Olsen,[1 7]

To cite: Li J, Cnattingus S, Gissler M, *et al*. The 5-minute Apgar score as a predictor of childhood cancer: a population-based cohort study in five million children. *BMJ Open* 2012;**0**:e001095. doi:10.1136/bmjopen-2012-001095

▸ Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-001095).

Received 1 March 2012
Accepted 2 July 2012

For numbered affiliations see end of article

Correspondence to
Dr Jiong Li; jl@soci.au.dk

ABSTRACT

Objective: The aetiology of childhood cancer remains largely unknown but recent research indicates that uterine environment plays an important role. We aimed to examine the association between the Apgar score at 5 min after birth and the risk of childhood cancer.

Design: Nationwide population-based cohort study.

Setting: Nationwide register data in Denmark and Sweden.

Study population: All live-born singletons born in Denmark from 1978 to 2006 (N=1 771 615) and in Sweden from 1973 to 2006 (N=3 319 573). Children were followed up from birth to 14 years of age.

Main outcome measures: Rates and HRs for all childhood cancers and for specific childhood cancers.

Results: A total of 8087 children received a cancer diagnosis (1.6 per 1000). Compared to children with a 5-min Apgar score of 9–10, children with a score of 0–5 had a 46% higher risk of cancer (adjusted HR 1.46, 95% CI 1.15 to 1.89). The potential effect of low Apgar score on overall cancer risk was mostly confined to children diagnosed before 6 months of age. Children with an Apgar score of 0–5 had higher risks for several specific childhood cancers including Wilms' tumour (HR 4.33, 95% CI 2.42 to 7.73).

Conclusions: A low 5 min Apgar score was associated with a higher risk of childhood cancers diagnosed shortly after birth. Our data suggest that environmental factors operating before or during delivery may play a role on the development of several specific childhood cancers.

ARTICLE SUMMARY

Article focus

- The aetiology of childhood cancer remains largely unknown but recent research indicates that uterine environment plays an important role.
- The Apgar score may have more implications than its role in current clinical practice.

Key messages

- A low 5 min Apgar score was associated with a higher risk of childhood cancer, suggesting that environmental factors operating before or during delivery may play a causal role.
- In addition to as an assessment tool for a newborn's clinical status, the Apgar score at 5 min may also indicate programming effect of fetal environment on diseases in later life, including childhood cancer.

Strengths and limitation of this study

- The most important strengths of our study include singletons in a prospectively longitudinal design, large sample size of five million, complete follow-up, accurate data on Apgar score and cancer diagnosis and detailed data on covariates.
- The limitations of our study are that we lack information on risk factors after birth and the case numbers for several childhood cancers are small.

INTRODUCTION

Childhood cancer is the second leading cause of deaths in children in high-income countries, and is of major concern for patients, families and societies.[1 2] In spite of extensive research, little is known about the aetiology of childhood cancer.[1 2] Almost half of childhood cancers are diagnosed before 5 years of age,[1] indicating that some of the causal factors operate in utero or in early postnatal life.[3 4] However, only few such risk factors have been identified.[5] Birth characteristics may represent the interactions between genetic susceptibility and prenatal environmental causes,[6–8] but the empirical evidence available to date is inconsistent and inconclusive.[6–9]

The Apgar score, which is assigned to virtually every newborn, evaluates the clinical state of the newborns based on five physical signs (heart rate, respiratory effort, reflex irritability, muscle tone and colour) present shortly after birth.[10] A total score of 9 or 10 indicates that the baby is 'in its best possible condition'.[10] Although the usefulness of the Apgar score has been questioned in recent

years,[11] this scoring system remains the only widely used and accepted tool for assessing the vitality of newborn infants across the world.[12 13] The 5 min Apgar score is a predictor of neonatal mortality,[14] and several neurological outcomes.[15–19] A suboptimal fetal environment[20] related to a low Apgar score may also be associated with compromised immune responses against tumours,[21] which can predict long-term health problems,[22 23] including future cancer risk.

In this population-based cohort study, we examined the association between the Apgar score at 5 min of age and childhood cancer, after taking other birth characteristics,[8 24] maternal socio-demographic characteristics,[1 2] and maternal smoking during pregnancy[25 26] into account. We hypothesised that children with a low Apgar score have a higher risk of childhood cancer than children with an optimal Apgar score.[21]

METHODS

Study design and study population

Data from eight national registers in Sweden and Denmark were linked by the unique personal identification number, which is assigned to each resident in the Scandinavian countries.[27] This population-based cohort study[28] included all singleton children born in Denmark from 1978 to 2006 (N=1 771 615) and in Sweden from 1973 to 2006 (N=3 319 573). Children were followed from birth until a cancer diagnosis, death, emigration, 14 years of age or end of follow-up (31 December 2006 in Sweden and 31 December 2007 in Denmark), whichever came first. The 610 children who had a birth defect and a cancer diagnosis were excluded, as some birth defects are closely associated with childhood cancers. The final study population included 5 091 188 children.

The Apgar score at 5 min of age and other birth characteristics (gestational age, birth weight, etc) were retrieved from Medical Birth Registers (MBR) in Denmark and in Sweden. The Danish Medical Birth Register was established in 1968[29] and the Swedish Medical Birth Register in 1973 (http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/10655/2003-112-3_20031123.pdf). These registers include data on practically all deliveries in Denmark and Sweden, respectively, and the information is collected from medical records in prenatal, delivery and neonatal care. It is compulsory for every healthcare provider to report to the registers.[30]

Socio-demographic factors were obtained from the Danish Integrated Database for Longitudinal Labor Market Research (IDA), the Danish Civil Registry System, the Swedish Education Registry and the Swedish Registry of Population and Population Changes.[28]

Outcome measurements

Data on cancer were obtained from national cancer registries, and the registration and coding practices have been described elsewhere.[31 32] The main outcomes of interest were all incident cancers (ICD-7 codes 104-205, ICD-10 codes C00-97) diagnosed before 15 years of age and the most frequent childhood cancers for which uterine environment has been suggested to play a role: [3 4 6–9] leukaemias (ICD-7 code 204, ICD-10 codes C91-95), lymphomas (ICD-7 code 201-203, ICD-10 code C81-C85), brain and nervous system tumours (ICD-7 code 193, ICD-10 codes C70-C72, C47, C74.1), retinoblastoma (ICD-7 code 192 and PAD 436, ICD-10 code C69.2), Wilms' tumour (ICD-7 code 180 and PAD 886, ICD-10 code C64.9), hepatoblastoma (ICD-7 code 155, ICD-10 code C22), malignant bone tumours (ICD-7 code 196, ICD-10 codes C40-C41) and testicular cancer (ICD-7 code 178, ICD-10 code C62).

Statistical analysis

All data handling and statistical analyses were performed using SAS V.9.2 statistical software package (SAS Institute, Inc, Cary, North Carolina, USA). The low Apgar score was categorised into each single score and also into two subgroups (0–5 and 6–8), as a very low score would be different from a score of over 5.[10] HRs with 95% CIs were estimated by Cox regression with the PHREG procedure. Potential confounders were included in the model, such as country (Denmark and Sweden), child sex (male and female) and birth characteristics (parity (1, 2 and ≥3), birth weight (<2500, 2500–3249, 3250–3999 and ≥4000 g), gestational age (<37 and ≥37 weeks), maternal factors (age (≤26, 27–30 and ≥31 years), education level (low: ≤9, middle: 10–14 and high: ≥15 years) (available Swedish data from 1990, 1995, 2000 and 2005, available annual Danish data from 1978 to 2006) and[29] smoking during pregnancy (yes, no) (available 1991–2007 in Denmark and 1983–2006 in Sweden)).

Analyses were performed when we excluded children diagnosed with cancer before 6 months of age to see how the overall effect of a low Apgar score would change when most embryonic cancers are excluded. We also repeated our analyses by dropping Wilms' tumour, hepatoblastoma, testicular cancer and retinoblastoma to see how the overall effect would be driven by these four childhood cancers.

Analyses were also stratified by country, sex, birth weight, gestational age and parity, which have been suggested to be associated with both Apgar score and cancer risk.[1 2] Analyses were also performed for the subcohorts where information on maternal smoking was available.

RESULTS

The baseline characteristics of the study population (5 061 798 singletons) are shown in table 1 according to the three subgroups of Apgar scores (0–5, 6–8 and 9–10). Low Apgar scores were comparable for most characteristics but more frequent among children born preterm or with low birth weight.

A total of 8087 children were diagnosed with cancer before 14 years of age (1.6 per 1000 children). Table 2

Table 1 Baseline characteristics of the study population according to the Apgar score*

Variables	Apgar score at 5 min 0–5	6–8	9–10	Unknown
Country				
Denmark	10673 (1)	42118 (2)	1669956 (96)	18868 (1)
Sweden	22694 (1)	116167 (4)	2951063 (90)	229649 (7)
Sex				
Boys	18829 (1)	89973 (3)	2365951 (91)	126011 (5)
Girls	14537 (1)	68312 (3)	2255068 (92)	122506 (5)
Birth order				
1	16910 (1)	91199 (4)	1971064 (90)	100239 (5)
2	9388 (1)	42290 (2)	1694866 (92)	93228 (5)
≥3	5782 (1)	23091 (2)	894631 (92)	484404 (5)
Unknown	1287 (2)	1705 (2)	60458 (86)	6646 (9)
Gestational age				
<37 weeks	8902 (4)	27338 (11)	191552 (79)	14439 (6)
>=37 weeks	22990 (<1)	129238 (3)	4368046 (92)	226668 (5)
Unknown	1475 (2)	1709 (2)	61421 (85)	7410 (10)
Birth weight (g)				
<2500	8238 (5)	22489 (13)	135895 (76)	11150 (6)
2500–3249	7766 (1)	39824 (3)	1137398 (91)	62399 (5)
3250–3999	10994 (<1)	65669 (2)	2448691 (92)	128267 (5)
>=4000	4340 (<1)	27736 (3)	833472 (92)	37497 (4)
Unknown	2029 (3)	2567 (3)	65563 (83)	9204 (12)
Maternal age				
<=26	12936 (1)	60051 (3)	1690721 (90)	120969 (6)
27–30	9293 (1)	45162 (3)	1378031 (92)	68490 (5)
≥31	11134 (1)	53060 (3)	1552002 (93)	59009 (4)
Unknown	4 (1)	12 (4)	265 (83)	39 (12)
Maternal education (years)				
Low (≤9)	16346 (1)	72583 (3)	2006475 (90)	146220 (7)
Middle (10–14)	8770 (1)	45007 (3)	1296875 (92)	52045 (4)
High (≥15)	5600 (1)	28120 (3)	908327 (93)	36363 (4)
Unknown	2651 (1)	12575 (3)	409342 (93)	13889 (3)
Maternal smoking during pregnancy†				
Yes	4755 (1)	21254 (3)	633618 (94)	10935 (2)
No	14661 (1)	85122 (3)	2419740 (95)	32303 (1)
Unknown	2395 (1)	9514 (4)	222589 (91)	9968 (4)

*Value is n (%). Study population includes all 5 091 188 singletons born in Denmark 1978–2006 and born in Sweden 1973–2006.
†Smoking status is available for 1991–2006 in Denmark and for 1983–2006 in Sweden.

Table 2 HRs for childhood cancer according to the Apgar score at 5 min

Apgar score	Cases (rate per 1000)	Crude HR	Adjusted HR (95% CI) †
0	3 (0.7)	0.47 (0.15 to 1.45)	0.56 (0.18 to 1.73)
1	15 (2.9)	2.44 (1.47 to 4.04)*	2.17 (1.31 to 3.60)*
2	6 (1.9)	1.89 (0.61 to 3.54)	1.72 (0.77 to 3.82)
3	9 (2.1)	1.85 (0.96 to 3.56)	1.67 (0.87 to 3.21)
4	14 (2.2)	1.61 (0.94 to 2.78)	1.48 (0.86 to 2.55)
5	21 (2.1)	1.40 (0.91 to 2.18)	1.32 (0.85 to 2.05)
0–5 combined	68 (2.0)	1.54 (1.21 to 1.96)*	1.46 (1.15 to 1.89)*
6	28 (1.5)	1.03 (0.71 to 1.49)	0.95 (0.66 to 1.38)
7	61 (1.6)	1.15 (0.99 to 1.34)	1.00 (0.77 to 1.29)
8	177 (1.7)	1.18 (1.08 to 1.29)	1.08 (0.93 to 1.26)
6–8 combined	266 (1.7)	1.12 (0.99 to 1.27)	1.05 (0.92 to 1.18)
9–10	7216 (1.6)	1.0 (ref)	1.0 (ref)

*p<0.05.
†Adjusted for country, sex, maternal factors at child birth (age, education and smoking during pregnancy) and birth characteristics of the child (birth weight, gestational age and birth order).

presents that children with a score of 0–5 had a higher overall rate of childhood cancer (2.0 per 1000) than those with a score of 6–8 (1.7 per 1000) and those with a score of 9–10 (1.6 per 1000). Compared to children with a 5 min Apgar score of 9–10, children with a score of 0–5 had a 46% increased risk of cancer before 14 years of age (adjusted HR 1.46, 95% CI 1.15 to 1.89), but children with a score of 6–8 had no increased risk of cancer (HR 1.05, 95% CI 0.92 to 1.18).

Table 3 shows that the HRs in children according to age at cancer diagnosis. For cancer diagnosed before 6 months of age, an Apgar score of 0–5 was associated with sixfold overall risk (HR 6.04, 95% CI 3.73 to 9.76) and an Apgar score of 6–8 was associated with a two-fold increase in risk (HR 2.17, 95% CI 1.54 to 3.05). The most frequent diagnosed cancers during this period include tumours from brain/nervous system, endocrinal glands, kidney and leukaemia/lymphomas (data not shown).There were no statistically significant increased risks for cancer diagnosed after 6 months of age.

Compared to children with an Apgar score of 9–10, children with a score of 0–5 had higher risks of several childhood cancers (CNS tumours, retinoblastoma, hepatic tumours, bone tumours and testicular tumours), but most estimates were not statistically significant (table 4). Low Apgar scores did not influence risks of lymphatic/hemapoietic neoplasms. The highest HR was observed in children with a score of 0–5 for Wilms' tumour (HR 4.33, 95% CI 2.42 to 7.73).

When Wilms' tumour, testicular cancer, hepatic cancer and retinoblastoma were not included in the analyses, the estimates for overall effect of a low Apgar score are smaller but the risks remain elevated (data not shown). With these exclusions, the estimates for cancer diagnosed before 6 months were even slightly higher (data not shown) than those presented in table 3. When we excluded cancers diagnosed during the first 6 months of life, a low Apgar score was not associated with increased overall cancer risk or with CNS cancer (data not shown). Estimates for other cancers, such as Wilms' tumour, remained essentially unchanged (data not shown).

The elevated risks related to an Apgar score of 0–5 were higher in almost all each stratum of the covariates, such as country (Denmark and Sweden), child sex (male and female) and birth characteristics (parity (1, 2 and ≥3), birth weight (<2500, 2500–3249, 3250–3999 and ≥4000 g), gestational age (<37 and ≥37 weeks)), maternal factors (age (≤26, 27–30 and ≥31 years), education level (low: ≤9, middle: 10–14 and high: ≥15 years)[29] and smoking during pregnancy (yes, no)) (data not shown).

DISCUSSION

Children with a low 5 min Apgar score, especially children with a score of 0–5, had a higher overall risk of childhood cancer that was diagnosed before 6 months of age. We also observed higher risks for several main childhood cancers like Wilms' tumour. The associations were independent of country, child sex, child birth characteristics (birth weight, birth order and gestational age) and maternal factors (age, education and smoking during pregnancy). However, we found no association between low Apgar score and risk of leukaemia and other lymphatic/haemapoietic malignancies.

The theory of 'developmental-origins of health and disease' proposes the importance of in utero environment for long-term human health.[22 23] We observed that children with a low Apgar score between 0 and 5 had a higher overall cancer risk than those with an optimal score (9 or 10). The mechanism underlying this observation is, however, unclear. A low Apgar score is a marker of a suboptimal fetal environment[20] or other factors that prevent the child from achieving a high score. From a programming perspective, it is interesting to observe that the effect of a low Apgar score on overall cancer risk was the strongest for cancers diagnosed before 6 months of age. Tumours from brain/nervous system, endocrinal glands, kidney and leukaemia/lymphomas were among the most frequent diagnosed cancers during this period. This observation is in line with suggestions from previous studies that in utero exposures to insulin-like

Table 3 HRs for childhood cancer according to the Apgar score at 5 min, by age at diagnosis

Age at diagnosis	Apgar score	Cases (rate, ‰)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Under 6 months	0–5	20 (0.6)	6.65 (4.15 to 10.65)*	6.04 (3.73 to 9.76)*
	6–8	39 (0.2)	2.43 (1.73 to 3.39)*	2.17 (1.54 to 3.05)*
	9–10	465 (0.1)	1.0 (ref)	1.0 (ref)
6 months–5 years	0–5	25 (0.9)	1.21 (0.82 to 1.79)	1.18 (0.80 to 1.76)
	6–8	134 (0.9)	1.15 (0.97 to 1.36)	1.09 (0.92 to 1.30)
	9–10	3678 (0.8)	1.0 (ref)	1.0 (ref)
>5 years	0–5	23 (1.0)	1.17 (0.78 to 1.77)	1.10 (0.73 to 1.65)
	6–8	93 (0.7)	0.89 (0.73 to 1.10)	0.83 (0.67 to 1.02)
	9–10	3223 (0.8)	1.0 (ref)	1.0 (ref)

*p<0.05.
†Adjusted for country, sex, maternal factors at child birth (age, education and smoking during pregnancy) and birth characteristics of the child (birth weight, gestational age and birth order).

Table 4 HRs for main childhood cancers according to the Apgar score at 5 min

Cancer type	Apgar score	Cancer cases (rate per 1000)	Crude HR (95% CI)	Adjusted HR† (95% CI)
Leukaemia	0–5	13 (0.4)	1.03 (0.60 to 1.79)	1.05 (0.61 to 1.81)
	6–8	71 (0.5)	1.02 (0.81 to 1.29)	1.02 (0.80 to 1.29)
	9–10	2122 (0.5)	1.0 (ref)	1.0 (ref)
Lymphomas	0–5	3 (0.1)	0.84 (0.27 to 2.60)	0.73 (0.23 to 2.27)
	6–8	12 (0.1)	0.62 (0.35 to 1.09)	0.51 (0.29 to 0.90)
	9–10	598 (0.1)	1.0 (ref)	1.0 (ref)
Central nervous system cancers	0–5	21 (0.6)	1.24 (0.78 to 1.98)	1.22 (0.77 to 1.94)
	6–8	104 (0.7)	1.29 (1.06 to 1.57)*	1.26 (1.03 to 1.54)*
	9–10	2432 (0.5)	1.0 (ref)	1.0 (ref)
Retinoblastoma	0–5	3 (0.1)	2.20 (0.70 to 6.84)	2.03 (0.64 to 6.39)
	6–8	4 (<0.05)	0.52 (0.19 to 1.39)	0.48 (0.18 to 1.28)
	9–10	240 (0.1)	1.0 (ref)	1.0 (ref)
Wilms' tumour	0–5	12 (0.4)	4.62 (2.61 to 8.20)*	4.33 (2.42 to 7.73)*
	6–8	18 (0.1)	1.24 (0.77 to 1.99)	1.16 (0.72 to 1.87)
	9–10	444 (0.1)	1.0 (ref)	1.0 (ref)
Hepatoblastoma	0–5	1 (<0.05)	1.78 (0.25 to 12.76)	1.51 (0.21 to 10.96)
	6–8	4 (<0.05)	1.27 (0.47 to 3.44)	1.06 (0.39 to 2.92)
	9–10	96 (<0.05)	1.0 (ref)	1.0 (ref)
Bone cancer	0–5	3 (0.1)	2.25 (0.72 to 7.02)	2.05 (0.65 to 6.45)
	6–8	6 (<0.05)	0.85 (0.38 to 1.90)	0.79 (0.35 to 1.80)
	9–10	220 (0.1)	1.0 (ref)	1.0 (ref)
Testicular cancer	0–5	0 (0)	–	–
	6–8	4 (<0.05)	2.08 (0.76 to 5.75)	1.89 (0.68 to 5.25)
	9–10	59 (<0.05)	1.0 (ref)	1.0 (ref)

*p<0.05.
†Adjusted for country, sex, maternal factors at child birth (age, education and smoking during pregnancy) and birth characteristics of the child (birth weight, gestational age and birth order).

growth factors,[8] oestrogens[33 34] or infections[24 35] may play a role for the relationships between other birth outcomes and many childhood cancers, or childhood cancer risk in general. A low Apgar score probably shares aetiology with cancers initiated in fetal life, and different biological pathways may operate for the association between Apgar score and childhood cancers. For example, neonatal treatments related to low Apgar scores may increase the risk of some childhood cancers.[36 37]

The best evidence for fetal origins of childhood cancer has been available for leukaemia.[7 8 38] Our findings suggest that those observations may operate through the mechanisms that do not affect the Apgar score, and similar interpretations apply to other lymphatic/haemapoietic neoplasms. The associations between a low Apgar score and several other specific childhood cancers in our study are noteworthy. For example, the highest risk of a low Apgar score was obtained for Wilms' tumour, which is in line with observations in two register-based studies (restricted to only girls in one of the studies)[39 40] but not in another case–control study.[41] Hypoxia, as indicated by a low score, may result in cell damage that subsequently leads to Wilms' tumour.[42 43] Alternatively, neonatal treatments provided to neonates with a low Apgar score may also increase the risk of Wilms' tumour.[36 37] Hepatoblastoma is reported to be associated with factors like low birth weight,[44] smoking during pregnancy or young maternal age.[45] A recent study showed a reverse association between birth order and retinoblastoma.[9] However, the observed elevated risks of both hepatoblastoma and retinoblastoma after adjustment might indicate an independent role of a low Apgar score for these two childhood cancers.

The observed associations between low Apgar scores and childhood cancer risk were not explained by other adverse birth outcomes, which have been widely used as the proxy indicators of fetal environment to explain fetal origins for a number of adult diseases.[22 23] As expected, a low Apgar score was more common among children with adverse birth outcomes, which often correlate with childhood cancers.[7–9 38] However, the elevated risks related to a low score were observed in almost all subgroups of baseline characteristics, including but not restricted to pregnancies with adverse birth outcomes. Furthermore, the associations were consistent according to country and maternal factors under investigation.

The most important strengths of our study include the prospective longitudinal design, large sample size and detailed data on other covariates. The registry system in the Nordic countries provides both a complete case ascertainment and accurate linkage with other data, which allow complete follow-up with least impact of misclassification error.[27] The rarity of childhood cancer makes population-based epidemiological

studies very difficult. Much of the heterogeneity of previous results might be due to the small sample sizes and lack of control for factors related to the child or the mother. Our data enabled us to do a more in-depth investigation by examining risks in subgroups. The cohort design based on prospectively collected high-quality data minimised the impact of information or recall bias.

One limitation of our study is that we lack information on risk factors after birth. However, factors associated with a low Apgar score, such as related neonatal treatments, may lie in the pathways between exposure and outcome, and should not necessarily be controlled for in the analyses.[46] A second limitation is that we cannot rule out the confounding of factors like environmental exposures after birth. Third, the case numbers for several childhood cancers are small, although the total population included over 5 million children.

To conclude, our findings support the developmental-origins hypothesis of childhood cancer. An association between a low Apgar score and childhood cancer does not prove a causal role of the components that make up the Apgar score but strengthens the relevance of viewing the prenatal time period as a causal time window of interest. A low Apgar score may reflect a pathological pregnancy that could share causes with childhood cancers, or childhood cancers may have a clinical onset that starts during fetal life. In the first situation, a low Apgar score may also be associated with cancer risk in adulthood. In addition to being a widely accepted assessment tool in neonatal care, the Apgar score may indicate programming effects of fetal environment on further health, suggesting that its role in clinical practice and public health may reach beyond its current use.

Author affiliations
[1]Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark
[2]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden
[3]National Institute for Health and Welfare, Helsinki, Finland/Nordic School of Public Health, Gothenburg, Sweden
[4]Section for General Practice, Department of Public Health, Aarhus University, Aarhus, Denmark
[5]Research Unit for General Practice, Department of Public Health, Aarhus University, Aarhus, Denmark
[6]Research Program for Mental Child Health, Department of Public Health, Aarhus University, Aarhus, Denmark
[7]Department of Epidemiology, School of Public Health, University of California, Los Angeles, USA

Contributors JL conceived the research, analysed the data and wrote the first draft of the manuscript. JL, SC, MG, MV, CO, JA and JO contributed to data analysis, interpretation of results and critical revision of the manuscript. All authors approved the final manuscript.

Funding This work was supported a grant by Dr Jiong Li from the European Research Council (ERC-2010-StG no. 260242, the European Union Seventh Framework Programme (EU FP7)); the Nordic Cancer Union (2008); the NordForsk (070331); the Danish Medical Research Council (projects no. 09-060229, 09-063494, and 09-072986); and the Swedish Council for Working Life and Social Research (Grant no. 2010-0092).

Competing interests None.

Ethics approval The study was approved by Danish Data Protection Agency (j nr. 2008-41-2680), Scientific Ethics Committee of Central Region Jylland (VEK, sagnr. M-20100252), Research Ethics Committee (EPN) at Karolinska Institutet (Ref no. 2008/4:6).

Patient consent Not needed for register-based research according to laws in Denmark and Sweden.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Kaatsch P. Epidemiology of childhood cancer. *Cancer Treat Rev* 2010;36:277–85.
2. Parkin DM, Whelan S, Ferlay J, *et al*. *Cancer incidence in five continents VIII*. Lyon, France: IARC Scientific Publications, 2002.
3. Anderson LM. Environmental genotoxicants/carcinogens and childhood cancer: bridgeable gaps in scientific knowledge. *Mutat Res* 2006;608:136–56.
4. Kimmel GL. An overview of children as a special population—relevance to predictive biomarkers. *Toxicol Appl Pharmacol* 2005;206:215–18.
5. Garner MJ, Turner MC, Ghadirian P, *et al*. Epidemiology of testicular cancer: an overview. *Int J Cancer* 2005;116:331–9.
6. Greaves M. Molecular genetics, natural history and the demise of childhood leukaemia. *Eur J Cancer* 1999;35:1941–53.
7. Ma X, Metayer C, Does MB, *et al*. Maternal pregnancy loss, birth characteristics, and childhood leukemia (United States). *Cancer Causes Control* 2005;16:1075–83.
8. Tower RL, Spector LG. The epidemiology of childhood leukemia with a focus on birth weight and diet. *Crit Rev Clin Lab Sci* 2007;44:203–42.
9. Von Behren J, Spector LG, Mueller BA, *et al*. Birth order and risk of childhood cancer: a pooled analysis from five US States. *Int J Cancer* 2011;128:2709–16.
10. Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg* 1953;32:260–7.
11. Use and abuse of the Apgar score. Committee on Fetus and Newborn, American Academy of Pediatrics, and Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. *Pediatrics* 1996;98:141–2.
12. Finster MMD, Wood MMD. The Apgar score has survived the test of time. *Anesthesiology* 2005;102:855–7.
13. Papile LA. The Apgar score in the 21st century. *N Engl J Med* 2001;344:519–20.
14. Casey BM, McIntire DD, Leveno KJ. The continuing value of the Apgar score for the assessment of newborn infants. *N Engl J Med* 2001;344:467–71.
15. Li J, Olsen J, Vestergaard M, *et al*. Low Apgar scores and risk of childhood attention deficit hyperactivity disorder. *J Pediatr* 2011;158:775–9.
16. Moster D, Lie RT, Irgens LM, *et al*. The association of Apgar score with subsequent death and cerebral palsy: a population-based study in term infants. *J Pediatrics* 2001;138:798–803.
17. Odd DE, Rasmussen F, Gunnell D, *et al*. A cohort study of low Apgar scores and cognitive outcomes. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F115–20.
18. Stuart A, Olausson PO, Kallen K. Apgar scores at 5 minutes after birth in relation to school performance at 16 years of age. *Obstet Gynecol* 2011;118:201–8.
19. Sun Y, Vestergaard M, Pedersen CB, *et al*. Apgar scores and long-term risk of epilepsy. *Epidemiology* 2006;17:296–301.
20. Gilstrap LC III, Hauth JC, Hankins GD, *et al*. Second-stage fetal heart rate abnormalities and type of neonatal acidemia. *Obstet Gynecol* 1987;70:191–5.
21. Ekbom A. The developmental environment and the early origins of cancer. In: Gluckman P, Hanson M. eds. *Developmental origins of health and disease*. Cambridge: Cambridge University Press, 2006:415–25.
22. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science* 2004;305:1733–6.
23. Gluckman PD, Hanson MA, Cooper C, *et al*. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008;359:61–73.
24. Greaves M. Childhood leukaemia. *BMJ* 2002;324:283–7.
25. Okasha M, McCarron P, Gunnell D, *et al*. Exposures in childhood, adolescence and early adulthood and breast cancer risk: a systematic review of the literature. *Breast Cancer Res Treat* 2003;78:223–76.

26. Park SK, Kang D, McGlynn KA, *et al*. Intrauterine environments and breast cancer risk: meta-analysis and systematic review. *Breast Cancer Res* 2008;10:R8.
27. Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;287:2398–9.
28. Li J, Vestergaard M, Obel C, *et al*. Cohort profile: the nordic perinatal bereavement cohort. *Int J Epidemiol* 2010;40:1161–7.
29. Knudsen LB, Olsen J. The Danish medical birth registry. *Dan Med Bull* 1998;45:320–3.
30. Axelsson O. The Swedish medical birth register. *Acta Obstet Gynecol Scand* 2003;82:491–2.
31. Barlow L, Westergren K, Holmberg L, *et al*. The completeness of the Swedish Cancer Register ΓÇô a sample survey for year 1998. *Acta Oncol* 2009;48:27–33.
32. Gjerstorff ML. The Danish cancer registry. *Scand J Public Health* 2011;39:42–5.
33. Petridou E, Panagiotopoulou K, Katsouyanni K, *et al*. Tobacco smoking, pregnancy estrogens, and birth weight. *Epidemiology* 1990;1:247–50.
34. Liehr JG. Is estradiol a genotoxic mutagenic carcinogen? *Endocr Rev* 2000;21:40–54.
35. Law GR. Host, family and community proxies for infections potentially associated with leukaemia. *Radiat Prot Dosimetry* 2008;132:267–72.
36. Sadetzki S, Mandelzweig L. Childhood exposure to external ionising radiation and solid cancer risk. *Br J Cancer* 2009;100:1021–5.
37. Spector LG, Klebanoff MA, Feusner JH, *et al*. Childhood cancer following neonatal oxygen supplementation. *J Pediatr* 2005;147:27–31.
38. Greaves M. Molecular genetics, natural history and the demise of childhood leukaemia. *Eur J Cancer* 1999;35:173–85.
39. Heuch JM, Heuch I, Kvale G. Birth characteristics and risk of Wilms' tumour: a nationwide prospective study in Norway. *Br J Cancer* 1996;74:1148–51.
40. Schuz J, Schmidt LS, Kogner P, *et al*. Birth characteristics and Wilms tumors in children in the Nordic countries: a register-based case-control study. *Int J Cancer* 2011;128:2166–73.
41. Puumala SE, Soler JT, Johnson KJ, *et al*. Birth characteristics and Wilms tumor in Minnesota. *Int J Cancer* 2008;122:1368–73.
42. Ruan K, Song G, Ouyang G. Role of hypoxia in the hallmarks of human cancer. *J Cell Biochem* 2009;107:1053–62.
43. Rankin EB, Giaccia AJ. The role of hypoxia-inducible factors in tumorigenesis. *Cell Death Differ* 2008;15:678–85.
44. Reynolds P, Urayama KY, Von Behren J, *et al*. Birth characteristics and hepatoblastoma risk in young children. *Cancer* 2004;100:1070–6.
45. McLaughlin CC, Baptiste MS, Schymura MJ, *et al*. Maternal and infant birth characteristics and hepatoblastoma. *Am J Epidemiol* 2006;163:818–28.
46. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd edn. Philadelphia: Lippincott Williams & Wilkins, 2008.