The Five-minute Apgar Score as a Predictor of Childhood Cancer: a Study in Five Million Children

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

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ABSTRACT

Objective: The etiology 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 minutes after birth and the risk of childhood cancer.

Design: Nationwide population-based cohort study

Setting: Nationwide register data in Denmark and Sweden

Study population: Alll live-born singletons born in Denmark from 1978 to 2006 (N=1,741,177) and in Sweden from 1973 to 2006 (N=3,319,621). Children were followed up from birth to 14 years of age.

Main outcome measures: Rates and hazard ratios (HRs) of all cancers and specific cancers.

Results: A total of 8697 children received a cancer diagnosis (1.7 per 1000). Compared to children with a 5-minute Apgar score of 9-10, children with a score of 0-5 had a 50% higher risk of cancer (adjusted hazard ratio (HR) 1.50, 95% confidence interval (CI) 1.19-1.89), whereas children with a score of 6-8 had a 14% higher risk (adjusted HR 1.14, 95% CI 1.02-1.28). These associations were not modified by country, sex, birth characteristics, and maternal factors. Children with a score of 0-5 had higher risks for most childhood cancers in general, but the confidence intervals for those estimates were often wide due to the small number of cases. The highest HR was 4.78 (95% CI 2.79- 8.19) for Wilms' tumor in children with an Apgar score of 0-5.

Conclusions: Our data shows that a low five-minute 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 minutes may also indicate programming effect of fetal environment on diseases in later life, including childhood cancer.

Key words the Apgar score at 5 minutes**,** cohort, developmental origins of disease, childhood cancer.

INTRODUCTION

Childhood cancer is the second leading cause of deaths in children in high income countries, and it is of major concern for patients, families, and societies. [1, 2] In spite of extensive research, little is known about the etiology of childhood cancer. [1, 2] Almost half of childhood cancers are diagnosed before 5 year of age,[1] indicating that some 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 of cancer, [6-8] but the empirical evidence available to date is inconsistent and inconclusive. [6-9]

The Apgar score is assigned to virtually every newborn, which evaluates the clinical state of the newborns based on five physical signs (heart rate, respiratory effort, reflex irritability, muscle tone, and color) 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 five-minute 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 tumors,[21] which can predict long-term human health, [22, 23] including future cancer risk.

In this population-based cohort study, we examined the association between the Apgar score at five minutes of age and childhood cancer, after taking into account other birth characteristics, [8, 24] maternal socio-demographic characteristics, [1, 2] and maternal smoking during pregnancy. [25, 26] We hypothesized that children with a low Apgar score have a higher risk of childhood cancer than children with a full 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] include all singleton children born in Denmark from 1978 to 2006 (N=1,741,177) and in Sweden from 1973 to 2006 (N=3,319,621). Children were followed from birth until a cancer diagnosis, death, emigration, 14 years of age, or end of follow up (December 31st, 2006 in Sweden, December 31st, 2007 in Denmark), whichever came first.

The Apgar score at 5 minutes 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 health care 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 was 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), and the most frequent childhood cancers: [3, 4] leukemia (ICD-7 code 204, ICD-10 codes C91-95), Hodgkin's lymphoma (ICD-7 code 201, ICD-10 code C81), non-Hodgkin's lymphoma (ICD-7 codes 200, 202, ICD-10 codes C82-83), Hepatic tumors (ICD-7 code 155, ICD-10 code C22), Testis cancer (ICD-7 code 178, ICD-10 code C62), Wilm's tumor (ICD-7 code 180 and PAD 886, ICD-10 code C64.9), retinoblastoma of the eye (ICD-7 code 192 and PAD 436, ICD-10 code C69.2), and central nervous system (CNS) tumors (ICD-7 code 193, ICD-10 codes C70-71).

Statistical analysis

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

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 sub-cohorts 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 3 subgroups of Apgar scores (0 to 5, 6-8, and 9-10). Low Apgar scores were more common among boys, first-born children, children born preterm or with low birth weight, children born to mothers with lower education or to mothers who smoked during pregnancy.

A total of 8697 children were diagnosed with cancer before 14 years of age (1.7 per 1000 children). Table 2 presents that children with a score of 0 to 5 had a higher overall rate of childhood cancer (2.3 per 1000) than those with a score of 6 to 8 (2.0 per 1000), and those with a score of 9 to 10 (1.7 per 1000). Compared to children with a five-minute Apgar score of 9-10, children with a score of 0-5 had a 50% increased risk of cancer before 14 years of age (adjusted Hazard ratio (HR) 1.50, 95% confidence interval (CI) 1.19-1.89), and children with a score of 6-8 had a 14% increased risk (HR 1.14, 95% CI 1.02-1.28).

Table 3 shows that the HRs in children with a score of 0-5 were higher in almost all strata, according to country, child's sex and birth characteristics (birth weight, gestational age, and birth order), and maternal factors (age, education, and smoking status during pregnancy).

Compared to children with a score of 9-10, children with a score of 0-5 had higher risks for several main childhood cancers (CNS tumors, retinoblastoma, hepatic tumors, bone tumors, and testicular tumors), 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' tumor (HR 4.78, 95% CI 2.79-8.19).

DISCUSSION

Children with a low 5-minute Apgar score, especially children with a score of 0 to 5, had a higher overall risk of childhood cancer and higher risks for several main childhood cancers. The association was independent of country, child sex, child birth characteristics (birth weight, birth order, and gestational age), and maternal factors (age, education, and smoking during pregnancy). Similar associations were seen for most childhood cancers, albeit the estimate was only statistically significant for Wilms' tumor. However, we found no association between low Apgar score and risk of leukemia and other lymphatic / hemapoietic malignancies.

The theory of 'developmental-origins of health and disease' proposes the importance of in utero environment in long term human health. [22, 23] We observed that children with any Apgar score between 0 and 8 at 5 minutes, especially those with a score of 0 to 5, had a higher overall cancer risk than those with an optimal score of 9 to 10. The mechanism underlying this observation is, however, unclear. It should be noted that the Apgar score is a sum of 5 signs (rating 0 to 2), which are not of equal value.[10, 13] A low Apgar score is a marker of the factors that prevent the child from achieving a high score, or a suboptimal fetal environment [20] that may have a programming effect on the development of childhood cancer. While in utero exposures to insulin-like growth factors,[8] estrogens, [33, 34] or infections [24, 35] have been proposed to explain the relationships between most of other birth outcomes and childhood cancer, different biological pathways may operate for the association between the Apgar score and childhood cancer. It can also be hypothesized that neonatal treatments related to low Apgar scores may increase the risk of some childhood cancers. [36, 37]

The observed associations between low Apgar scores and childhood cancer risk were not explained by the role of 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 cancer. [6-9] However, the elevated risks related to a low score were observed in almost all subgroups, not restricted to adverse birth outcomes. Furthermore, the associations were consistent according to country and maternal factors under investigation.

The best evidence for fetal origins of childhood cancer has been available for leukemia. [6-8] But our findings suggest that those observations may operate through the mechanisms that do not affect the Apgar score. Similar interpretations apply to other lymphatic / hemapoietic neoplasms, and CNS tumors. The associations between a low Apgar score and several specific childhood cancers in our study are noteworthy. For example, the highest risk of a low Apgar score was obtained for Wilms tumor, which is in line with observations in two register-based studies (restricted to only girls in one of the studies) [38, 39] but not in another case-control study. [40] Hypoxia, as indicated by a low score, may result in cell damage that subsequently leads to Wilms tumor.[41, 42] Alternatively, neonatal treatments provided to neonates with a low Apgar score may also increase the risk of Wilms tumor. [36, 37] Hepatoblastoma is reported to be associated with factors like low birth weight,[43] smoking during pregnancy or young maternal age.[44] 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 most important strengths of our study include singletons in a prospectively longitudinal design, large sample size, complete follow up, and detailed data on other covariates. 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 both

factors related to the child and the mother. Our data enabled us to do more in-depth investigation by examining the risks in subgroups. The cohort design based on prospectively collected high quality data minimized the impact of information bias or recall bias. 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]

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.[45] Second limitation is that we cannot rule out the confounding of factors like environmental exposures after birth. Thirdly, 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 it will further strengthen the relevance of viewing the prenatal time period as a causal time window of interest. A low Apgar score may reflect a pathologic pregnancy which 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.

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Competing Interests None.

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.

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.

Data sharing statement There are no additional data available.

ARTICLE SUMMARY

Article focus

- The etiology 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 five-minute 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 minutes 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 5 million, complete follow up, accurate data on exposure and outcome, 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.

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

Variables	Apgar score at 5 minutes			
	0-5	6-8	9-10	Unknown
Country				
Denmark	10,677 (32)	42,151 (27)	1,670,475 (36)	19,874 (8)
Sweden	22,698 (68)	116,177 (73)	2,951,093 (64)	229,653 (92)
Sex				
Boys	18,834 (56)	90,003 (57)	2,366,258 (51)	126,014 (51)
Girls	14,540 (44)	68,325 (43)	2,255,310 (49)	122,513 (49)
Birth order				
1	16,915 (51)	91,222 (58)	1,971,289 (43)	100,242 (40)
2	9389 (28)	42,300 (27)	1,695,084 (37)	93,232 (38)
≥3	5783 (17)	23,099 (15)	984,716 (19)	448,407 (19)
Unknown	1288 (4)	1707 (1)	60,479 (1)	6646 (3)
Gestational age				
<37 weeks	8903 (27)	27,348 (17)	191,587 (4)	14,441 (6)
>=37 weeks	22,997 (69)	129,270 (82)	4,368,538 (95)	226,676 (91)
Unknown	1475 (4)	1710 (1)	61,443 (1)	7410 (3)
Birth weight (g)				
<2500	8240 (25)	22,495 (14)	135,925 (3)	11,152 (4)
2500-3249	7766 (23)	39,838 (25)	1,137,533 (25)	62,402 (25)
3250-3999	10,998 (33)	65,683 (41)	2,448,948 (53)	128,269 (52)

>=4000	4341 (13)	27,742 (18)	833,578 (18)	37,499 (15)
Unknown	2030 (6)	2570 (2)	65,584 (1)	9205 (4)
Maternal age				
<=26	12,939 (39)	60,066 (38)	1,690,935 (37)	120,974 (49)
27-30	9295 (28)	45,174 (29)	1,378,188 (30)	68,491 (28)
≥31	11,137 (33)	53,076 (34)	1,552,180 (34)	59,023 (24)
Unknown	4 (<1)	12 (<1)	265 (<1)	39 (<1)
Maternal education (years)				
Low (≤9)	16,349 (49)	72,598 (46)	2,006,645 (43)	146,227 (59)
Middle (10-14)	8775 (26)	45,018 (28)	1,297,059 (28)	52,047 (21)
High (≥15)	5600 (17)	28,130 (18)	908,454 (20)	36,363 (15)
Unknown	2651 (8)	12,582 (8)	409,410 (9)	13,890 (6)
Maternal smoking during pregnancy[†]				
Yes	4756 (22)	21,260 (18)	633,236 (19)	10,937 (21)
No	14,667 (62)	85,130 (73)	2,419,935 (74)	32,305 (61)
Unknown	2385 (11)	9517 (8)	222,604 (7)	9968 (19)

[*] Value is n (%). Study population includes all 5,061,798 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.

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Table 2. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes.

Apgar score	Cases (rate per 1000)	Crude HR	Adjusted HR (95%CI) *	Adjusted HR 95%CI) †
0	3 (0.7)	0.44 (0.14-1.36) ‡	0.47 (0.15-1.45) ‡	0.46 (0.15-1.43) ‡
1	15 (2.9)	2.28 (1.38-3.78) ‡	2.20 (1.32-3.65) ‡	2.15 (1.30-3.57) ‡
2	7 (2.3)	1.47 (0.61-3.54)	1.44 (0.60-3.45)	1.37 (0.57-3.29)
3	11 (2.6)	2.13 (1.18-3.84) ‡	2.06 (1.14-3.72) ‡	1.96 (1.08-3.54) ‡
4	14 (2.2)	1.52 (0.88-2.61)	1.48 (0.86-2.54)	1.41 (0.82-2.42)
5	26 (2.5)	1.65 (1.11-2.44) ‡	1.62 (1.10-2.40) ‡	1.56 (1.05-2.31) ‡
0-5 combined	***76 (2.3)***	***1.57 (1.25-1.98)*** ‡	***1.56 (1.23-1.96)*** ‡	***1.50 (1.19-1.89)*** ‡
6	34 (1.8)	1.17 (0.84-1.64)	1.15 (0.82-1.34)	1.10 (0.78-1.54)
7	67 (1.8)	1.07 (0.84-1.37)	1.05 (0.82-1.34)	1.01 (0.79-1.29)
8	208 (2.1)	1.26 (1.10-1.45) ‡	1.23 (1.07-1.42) ‡	1.20 (1.04-1.38) ‡
6-8 combined	***309 (2.0)***	***1.21 (1.07-1.35)*** ‡	***1.18 (1.05-1.32)***	***1.14 (1.02-1.28)***
9-10	***7765 (1.7)***	***1.0 (ref)***	***1.0 (ref)***	***1.0 (ref)***

*Adjusted for country, sex, and maternal factors at child birth (age, education, and smoking during pregnancy).

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†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, birth order).

‡ P<0.05.

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Table 3. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes, stratified on country, birth characteristics and maternal variables.

Variable		Apgar score	Cancer cases (rate, per 1000)	Crude HR* (95%CI)	Adjusted HR† (95%CI)
Country	Denmark	1-5	20 (1.9)	1.57 (1.25-1.98) ‡	1.52 (1.23-1.91) ‡
		6-8	72 (1.7)	1.21 (1.07-1.35) ‡	1.16 (1.03-1.30) ‡
		9-10	2461 (1.5)	1.0 (ref)	1.0 (ref)
	Sweden	1-5	56 (2.5)	1.65 (1.26-2.15) ‡	1.60 (1.23-2.09) ‡
		6-8	237 (2.0)	1.26 (1.06-1.38) ‡	1.16 (1.02-1.33) ‡
		9-10	5304 (1.8)	1.0 (ref)	1.0 (ref)
Sex	Male	1-5	44 (2.6)	1.54 (1.13-2.08) ‡	1.46 (1.07-1.99) ‡
		6-8	169 (1.9)	1.09 (0.94-1.28)	1.04 (0.89-1.22)
		9-10	4232 (1.8)	1.0 (ref)	1.0 (ref)
	Female	1-5	32 (2.5)	1.60 (1.12-2.29) ‡	1.55 (1.08-2.23) ‡
		6-8	140 (2.0)	1.35 (1.14-1.60) ‡	1.29 (1.09-1.53) ‡
		9-10	3533 (1.6)	1.0 (ref)	1.0 (ref)
Birth order	1	1-5	38 (2.5)	1.45 (1.04-2.02) ‡	1.38 (0.99-1.93)

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		6-8	174 (2.0)	1.14 (0.98-1.33)	1.10 (0.94-1.28)
		9-10	3385 (1.6)	1.0 (ref)	1.0 (ref)
	2	1-5	16 (1.7)	1.28 (0.78-2.09)	1.18 (0.72-1.93)
		6-8	72 (1.7)	1.08 (0.85-1.36)	0.99 (0.78-1.26)
		9-10	2797 (1.7)	1.0 (ref)	1.0 (ref)
	3	1-5	16 (2.8)	2.11 (1.29-3.46) ‡	2.13 (1.29-3.49) ‡
		6-8	59 (2.6)	1.63 (1.26-2.12) ‡	1.60 (1.23-2.09) ‡
		9-10	1480 (1.7)	1.0 (ref)	1.0 (ref)
Gestational age	<37 weeks	1-5	17 (1.9)	1.53 (1.16-2.00) ‡	1.48 (1.13-1.94) ‡
		6-8	63 (2.6)	1.16 (1.02-1.32) ‡	1.12 (0.99-1.28)
		9-10	353 (1.8)	1.0 (ref)	1.0 (ref)
	≥37 weeks	1-5	57 (2.5)	1.74 (1.07-2.84) ‡	1.71 (1.04-2.79) ‡
		6-8	244 (1.9)	1.34 (1.02-1.75) ‡	1.30 (0.99-1.71)
		9-10	7304 (1.7)	1.0 (ref)	1.0 (ref)
Birth weight	<2500 g	1-5	13 (1.6)	1.65 (0.94-2.88)	1.52 (0.86-2.66)
		6-8	46 (2.0)	1.32 (0.96-1.81)	1.20 (0.87-1.65)
		9-10	235 (1.7)	1.0 (ref)	1.0 (ref)

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	2500-3249g	1-5	18 (2.3)	1.54 (0.95-2.48)	1.50 (0.93-2.41)
		6-8	88 (2.2)	1.39 (1.12-1.73) ‡	1.33 (1.07-1.66) ‡
		9-10	1802 (1.6)	1.0 (ref)	1.0 (ref)
	3250-3999g	1-5	28 (2.5)	1.56 (1.07-2.28) ‡	1.51 (1.04-2.21) ‡
		6-8	126 (1.9)	1.20 (1.00-1.43) ‡	1.15 (0.96-1.37)
		9-10	4079 (1.7)	1.0 (ref)	1.0 (ref)
	≥4000 g	1-5	10 (2.3)	1.22 (0.63-2.34)	1.18 (0.61-2.26)
		6-8	44 (1.6)	0.89 (0.66-1.20)	0.86 (0.63-1.16)
		9-10	1536 (1.8)	1.0 (ref)	1.0 (ref)
Maternal age	<=26	1-5	30 (2.3)	1.50 (1.04-2.18) ‡	1.42 (0.98-2.06)
		6-8	114(1.9)	1.09 (0.90-1.31)	1.03 (0.85-1.25)
		9-10	3051 (1.8)	1.0 (ref)	1.0 (ref)
	27-30	1-5	24 (2.6)	1.73 (1.14-2.64) ‡	1.73 (1.13-2.63) ‡
		6-8	101(2.2)	1.42 (1.16-1.73) ‡	1.39 (1.13-1.70) ‡
		9-10	2271 (1.6)	1.0 (ref)	1.0 (ref)
	≥31	1-5	22 (2.0)	1.53 (1.01-2.33) ‡	1.42 (0.93-2.17)
		6-8	94 (1.8)	1.17 (0.95-1.44)	1.08 (0.87-1.33)

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		9-10	2443 (1.6)	1.0 (ref)	1.0 (ref)
Maternal education	Low	1-5	43 (2.6)	1.77 (1.30-2.39) ‡	1.67 (1.23-2.27) ‡
		6-8	164 (2.3)	1.27 (1.08-1.49) ‡	1.20 (1.03-1.41) ‡
		9-10	3692 (1.8)	1.0 (ref)	1.0 (ref)
	Middle	1-5	17 (1.9)	1.30 (0.80-2.13)	1.25 (0.76-2.06)
		6-8	62 (1.4)	0.88 (0.68-1.13)	0.84 (0.65-1.08)
		9-10	2155 (1.7)	1.0 (ref)	1.0 (ref)
	High	1-5	8 (1.4)	1.57 (1.22-2.02) ‡	1.48 (1.15-1.92) ‡
		6-8	64 (2.3)	0.97 (0.46-2.04)	0.95 (0.45-2.01)
		9-10	1357 (1.5)	1.0 (ref)	1.0 (ref)
Maternal smoking	Yes	1-5	6 (1.3)	0.89 (0.40-1.99)	0.86 (0.38-1.92)
		6-8	48 (2.3)	1.36 (1.02-1.82) ‡	1.28 (0.96-1.72)
		9-10	1074 (1.7)	1.0 (ref)	1.0 (ref)
	No	1-5	40 (2.7)	2.10 (1.53-2.88) ‡	2.07 (1.51-2.85) ‡
		6-8	144 (1.7)	1.17 (0.99-1.38)	1.10 (0.93-1.30)
		9-10	3629 (1.5)	1.0 (ref)	1.0 (ref)

*Crude analysis.

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[†]Adjusted for country, sex, maternal factors (age, education, and smoking during pregnancy), and birth characteristics of the child (birth weight, gestational age, and birth order).

[‡] P<0.05.

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Table 4. Hazard Ratios (HRs) for main childhood cancers according to the Apgar score at 5 minutes

Cancer type	Apgar score	Cancer cases (rate per 1000)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)
Leukemia	0-5	13 (0.4)	0.93 (0.54-1.64)	0.96 (0.55-1.65)	0.98 (0.57-1.69)
	6-8	85 (0.5)	1.13 (0.91-1.41) ‡	1.15 (0.93-1.43)	1.15 (0.93-1.43)
	9-10	2314 (0.5)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Hodgkin's disease	0-5	0 (-)	-	-	-
	6-8	2(<0.05)	0.49 (0.12-1.99)	0.44 (0.11-1.76)	0.42 (0.10-1.71)
	9-10	126 (<0.05)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Hodgkin's disease	0-5	3 (0.1)	1.12 (0.36-3.49)	1.04 (0.33-3.23)	0.97 (0.31-3.02)
	6-8	10 (0.1)	0.69 (0.37-1.29)	0.58 (0.31-1.09)	0.55 (0.29-1.03)
	9-10	449 (0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)
CNS cancers	0-5	20 (0.6)	1.22 (0.76-1.96)	1.21 (0.75-1.94)	1.18 (0.73-1.90)
	6-8	104 (0.7)	1.34 (1.10-1.63) ‡	1.31 (1.08-1.60) ‡	1.29 (1.06-1.58) ‡
	9-10	2345 (0.5)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Retinblastoma	0-5	3 (0.1)	2.01 (0.64-6.27)	1.97 (0.63-6.14)	1.85 (0.59-5.80)
	6-8	9 (0.1)	1.07 (0.55-2.07)	1.07 (0.55-2.08)	0.99 (0.50-1.93)

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	9-10	263 (0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Wilms' tumor	0-5	14 (0.4)	4.98 (2.93-8.47) ‡	4.92 (2.89-8.38) ‡	4.78 (2.79-8.19) ‡
	6-8	20 (0.1)	1.27 (0.81-1.99)	1.25 (0.80-1.96)	1.22 (0.78-1.91)
	9-10	484 (0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Hepatoblastoma	0-5	2 (0.1)	3.24 (0.80-13.12)	3.23 (0.80-13.07)	2.64 (0.65-10.86)
	6-8	5 (<0.05)	1.44 (0.59-3.53)	1.42 (0.58-3.49)	1.22 (0.49-3.02)
	9-10	107 (<0.05)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Bone cancer	0-5	3 (0.1)	2.00 (0.64-6.23)	2.03 (0.65-6.34)	1.87 (0.60-5.88)
	6-8	7 (<0.05)	0.88 (0.41-1.86)	0.89 (0.42-1.90)	0.85 (0.40-1.82)
	9-10	248 (0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Testicular cancer	0-5	0 (0)	-	-	-
	6-8	5 (<0.05)	2.44 (0.98-6.07)	2.23 (0.90-5.55)	2.15 (0.86-5.42)
	9-10	64 (<0.05)	1.0 (ref)	1.0 (ref)	1.0 (ref)

*Adjusted for country, sex, and maternal factors at child birth (age, education, and smoking during pregnancy).

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

‡ P<0.05.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4,5*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	4

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15,16
		(b) Indicate number of participants with missing data for each variable of interest	15,16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	15,16
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 15-25
		(*b*) Report category boundaries when continuous variables were categorized	6,15-25
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6,15-25
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15-25
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9,10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The Five-minute Apgar Score as a Predictor of Childhood Cancer: a population-based Cohort Study in Five Million Children

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

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ABSTRACT

Objective: The etiology 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 minutes 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 hazard ratios (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-minute Apgar score of 9-10, children with a score of 0-5 had a 46% higher risk of cancer (adjusted hazard ratio (HR) 1.46, 95% confidence interval (CI) 1.15-1.89). 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' tumor (HR 4.33, 95% CI 2.42-7.73).

Conclusions: A low five-minute 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.

Key words the Apgar score at 5 minutes**,** cohort, developmental origins of disease, childhood cancer.

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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 etiology of childhood cancer. [1, 2] Almost half of childhood cancers are diagnosed before 5 year 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 color) 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 five-minute 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 tumors,[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 five minutes 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 hypothesized that children with a low Apgar score have a higher risk of childhood cancer than children with an optimal Apgar score. [21]

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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 (December 31st, 2006 in Sweden, December 31st, 2007 in Denmark), whichever came first. The 610 children who had both 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 minutes 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 health care 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

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Data on cancer was 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] leukemias (ICD-7 code 204, ICD-10 codes C91-95), lymphomas (ICD-7 code 201-203, ICD-10 code C81-C85), brain and nervous system tumors (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' tumor (ICD-7 code 180 and PAD 886, ICD-10 code C64.9), hepatoblastoma (ICD-7 code 155, ICD-10 code C22), malignant bone tumors (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 version 9.2 statistical software package (SAS Institute, Inc., Cary, North Carolina). The low Apgar score was categorized into each single score and also into 2 subgroups (0-5 and 6-8), as a very low score would be different from a score of over 5. [10] Hazards ratios with 95% confidence intervals were estimated by Cox regression with the PHREG procedure. Potential confounders were included in the model, such as country (Denmark, Sweden), child sex (male, female) and birth characteristics ((parity (1, 2, ≥3), birth weight (<2500 g, 2500-3249 g, 3250-3999 g, and ≥4000 g), gestational age (<37 weeks and ≥37 weeks)), maternal factors ((age (≤26 years, 27-30 years, and ≥31years), education level (low: ≤9 years, middle:10-14 years, and high: ≥15 years) (available Swedish data from 1990,1995, 2000, and 2005, available annual Danish data from 1978-2006),[29] smoking during pregnancy (yes, no) (available 1991-2007 in Denmark and 1983-2006 in Sweden)).

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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' tumor, hepatoblastoma, testicular cancer, and retinoblastoma to see how the overall effect would be driven by these 4 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 sub-cohorts where information on maternal smoking was available.

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RESULTS

The baseline characteristics of the study population (5,061,798 singletons) are shown in Table 1 according to the 3 subgroups of Apgar scores (0 to 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 presents that children with a score of 0 to 5 had a higher overall rate of childhood cancer (2.0 per 1000) than those with a score of 6 to 8 (1.7 per 1000), and those with a score of 9 to 10 (1.6 per 1000). Compared to children with a five-minute 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 Hazard ratio (HR) 1.46, 95% confidence interval (CI) 1.15-1.89), but children with a score of 6-8 had no increased risk of cancer (HR 1.05, 95% CI 0.92-1.18).

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 6-fold overall risk (HR 6.04, 95% CI 3.73-9.76) and an Apgar score of 6-8 was associated with a two-fold increase in risk (HR 2.17, 95% CI 1.54-3.05). The most frequent diagnosed cancers during this period include tumors from brain/nervous system, endocrinal glands, kidney, and leukemia/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 for several childhood cancers (CNS tumors, retinoblastoma, hepatic tumors, bone tumors, and testicular tumors), but most estimates were not statistically significant (Table 4). Low Apgar scores did not

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influence risks of lymphatic / hemapoietic neoplasms. The highest HR was observed in children with a score of 0-5 for Wilms' tumor (HR 4.33, 95% CI 2.42-7.73).

When Wilms' tumor, 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' tumor, 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, Sweden), child sex (male, female) and birth characteristics ((parity (1, 2, ≥3), birth weight (<2500 g, 2500-3249 g, 3250-3999 g, and ≥4000 g), gestational age (<37 weeks and ≥37 weeks)), maternal factors ((age (≤26 years, 27-30 years, and ≥31years), education level (low: ≤9 years, middle:10-14 years, and high: ≥15 years),[29] and smoking during pregnancy (yes, no))(data not shown).

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DISCUSSION

Children with a low 5-minute Apgar score, especially children with a score of 0 to 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' tumor. 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 leukemia and other lymphatic / hemapoietic 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 to 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. Tumors from brain/nervous system, endocrinal glands, kidney, and leukemia/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 growth factors,[8] estrogens, [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 etiology 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]

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The best evidence for fetal origins of childhood cancer has been available for leukemia. [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 / hemapoietic 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' tumor, 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' tumor.[42, 43] Alternatively, neonatal treatments provided to neonates with a low Apgar score may also increase the risk of Wilms' tumor. [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

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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 minimized 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 pathologic pregnancy which 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.

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Competing Interests None.

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.

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).

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ARTICLE SUMMARY

Article focus

- The etiology 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 five-minute 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 minutes 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 5 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.

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

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Variables	Apgar score at 5 minutes			
	0-5	6-8	9-10	Unknown
Country				
Denmark	10,673 (1)	42,118 (2)	1,669,956 (96)	18,868 (1)
Sweden	22,694 (1)	116,167 (4)	2,951,063 (90)	229,649 (7)
Sex				
Boys	18,829 (1)	89,973 (3)	2,365,951(91)	126,011 (5)
Girls	14,537 (1)	68,312 (3)	2,255,068 (92)	122,506 (5)
Birth order				
1	16,910 (1)	91,199 (4)	1,971,064 (90)	100,239 (5)
2	9388 (1)	42,290 (2)	1,694,866 (92)	93,228 (5)
≥3	5782 (1)	23,091 (2)	894,631 (92)	484,404 (5)
Unknown	1287 (2)	1705 (2)	60,458 (86)	6646 (9)
Gestational age				
<37 weeks	8902 (4)	27,338 (11)	191,552 (79)	14,439 (6)
>=37 weeks	22,990 (<1)	129,238 (3)	4,368,046 (92)	226,668 (5)
Unknown	1475 (2)	1709 (2)	61,421 (85)	7410 (10)
Birth weight (g)				
<2500	8238 (5)	22,489 (13)	135,895 (76)	11,150 (6)
2500-3249	7766 (1)	39,824 (3)	1,137,398 (91)	62,399 (5)
3250-3999	10,994 (<1)	65,669 (2)	2,448,691 (92)	128,267 (5)
>=4000	4340 (<1)	27,736 (3)	833,472 (92)	37,497 (4)

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Unknown	2029 (3)	2567 (3)	65,563 (83)	9204 (12)
Maternal age				
<=26	12,936 (1)	60,051 (3)	1,690,721 (90)	120,969 (6)
27-30	9293 (1)	45,162 (3)	1,378,031 (92)	68,490 (5)
≥31	11,134 (1)	53,060 (3)	1,552,002 (93)	59,009 (4)
Unknown	4 (1)	12 (4)	265 (83)	39 (12)
Maternal education (years)				
Low (≤9)	16,346 (1)	72,583 (3)	2,006,475 (90)	146,220 (7)
Middle (10-14)	8770 (1)	45,007 (3)	1,296,875 (92)	52,045 (4)
High (≥15)	5600 (1)	28,120 (3)	908,327 (93)	36,363 (4)
Unknown	2651 (1)	12,575 (3)	409,342 (93)	13,889 (3)
Maternal smoking during pregnancy[†]				
Yes	4755 (1)	21,254 (3)	633,618 (94)	10,935 (2)
No	14,661 (1)	85,122 (3)	2,419,740 (95)	32,303 (1)
Unknown	2395 (1)	9514 (4)	222,589 (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.

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Table 2. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes.

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

* 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, birth order).

† P<0.05.

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Table 3. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes, by age at diagnosis.

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

*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).

† P<0.05.

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Table 4. Hazard Ratios (HRs) for main childhood cancers according to the Apgar score at 5 minutes

Cancer type	Apgar score	Cancer cases (rate per 1000)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Leukemia	0-5	13 (0.4)	1.03 (0.60-1.79)	1.05 (0.61-1.81)
	6-8	71 (0.5)	1.02 (0.81-1.29)	1.02 (0.80-1.29)
	9-10	2122 (0.5)	1.0 (ref)	1.0 (ref)
Lymphomas	0-5	3 (0.1)	0.84 (0.27-2.60)	0.73 (0.23-2.27)
	6-8	12 (0.1)	0.62 (0.35-1.09)	0.51 (0.29-0.90)
	9-10	598 (0.1)	1.0 (ref)	1.0 (ref)
CNS cancers	0-5	21 (0.6)	1.24 (0.78-1.98)	1.22 (0.77-1.94)
	6-8	104 (0.7)	1.29 (1.06-1.57) †	1.26 (1.03-1.54) †
	9-10	2432 (0.5)	1.0 (ref)	1.0 (ref)
Retinoblastoma	0-5	3 (0.1)	2.20 (0.70-6.84)	2.03 (0.64-6.39)
	6-8	4 (<0.05)	0.52 (0.19-1.39)	0.48 (0.18-1.28)
	9-10	240 (0.1)	1.0 (ref)	1.0 (ref)
Wilms' tumor	0-5	12 (0.4)	4.62 (2.61-8.20) †	4.33 (2.42-7.73) †
	6-8	18 (0.1)	1.24 (0.77-1.99)	1.16 (0.72-1.87)

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	9-10	444 (0.1)	1.0 (ref)	1.0 (ref)
Hepatoblastoma	0-5	1 (<0.05)	1.78 (0.25-12.76)	1.51 (0.21-10.96)
	6-8	4 (<0.05)	1.27 (0.47-3.44)	1.06 (0.39-2.92)
	9-10	96 (<0.05)	1.0 (ref)	1.0 (ref)
Bone cancer	0-5	3 (0.1)	2.25 (0.72-7.02)	2.05 (0.65-6.45)
	6-8	6 (<0.05)	0.85 (0.38-1.90)	0.79 (0.35-1.80)
	9-10	220 (0.1)	1.0 (ref)	1.0 (ref)
Testicular cancer	0-5	0 (0)	-	-
	6-8	4 (<0.05)	2.08 (0.76-5.75)	1.89 (0.68-5.25)
	9-10	59 (<0.05)	1.0 (ref)	1.0 (ref)

* 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, birth order).

† P<0.05.

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

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ABSTRACT

Objective: The etiology 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 minutes 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~~l~~ live-born singletons born in Denmark from 1978 to 2006 (N=1,774~~1~~1,615~~177~~) and in Sweden from 1973 to 2006 (N=3,319,573~~621~~). Children were followed up from birth to 14 years of age.

Main outcome measures: Rates and hazard ratios (HRs) ~~o~~for all childhood cancers and for specific childhood cancers.

Results: A total of 8087~~697~~ children received a cancer diagnosis (1.6~~7~~ per 1000). Compared to children with a 5-minute Apgar score of 9-10, children with a score of 0-5 had a 46~~50~~% higher risk of cancer (adjusted hazard ratio (HR) 1.46~~50~~, 95% confidence interval (CI) 1.15~~9~~-1.89~~), whereas children with a score of 6-8 had a 14% higher risk (adjusted HR 1.14, 95% CI 1.02-1.28)~~). The potential effect of low Apgar score on overall cancer risk was mostly confined to children diagnosed before 6 months of age~~. ~~These associations were not modified by country, sex, birth characteristics, and maternal factors~~. Children with an Apgar score of 0-5 had higher risks for several specific ~~most~~ childhood cancers including Wilms' tumor (HR ~~in general, but the confidence intervals for those estimates were often wide due to the small number of cases. The highest HR was~~ 4.33~~78, (~~(95% CI 2.42~~79~~-78.73~~19~~) ~~for Wilms' tumor in children with an Apgar score of 0-5~~.

Conclusions: ~~Our data shows that~~ A ~~a~~low five-minute Apgar score wa~~was~~s associated with a higher risk of childhood cancers diagnosed shortly after birth. Our data ~~childhood cancer,~~ suggest~~ing~~ that

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environmental factors operating before or during delivery may play a ~~causal~~ role on the development of several specific childhood cancers. ~~In addition to as an assessment tool for a newborn's clinical status, the Apgar score at 5 minutes may also indicate programming effect of fetal environment on diseases in later life, including childhood cancer.~~

Key words the Apgar score at 5 minutes, cohort, developmental origins of disease, childhood cancer.

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INTRODUCTION

Childhood cancer is the second leading cause of deaths in children in high income countries, and it is of major concern for patients, families, and societies.[1, 2] In spite of extensive research, little is known about the etiology of childhood cancer.[1, 2] Almost half of childhood cancers are diagnosed before 5 year 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 of cancer,[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, which evaluates the clinical state of the newborns based on five physical signs (heart rate, respiratory effort, reflex irritability, muscle tone, and color) 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 five-minute 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 tumors,[21] which can predict long-term human health problems,[22, 23] including future cancer risk.

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

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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~~27~~] This population-based cohort study[28~~28~~] included all singleton children born in Denmark from 1978 to 2006 (N=1,774~~1~~1,615~~177~~) and in Sweden from 1973 to 2006 (N=3,319,573~~621~~). Children were followed from birth until a cancer diagnosis, death, emigration, 14 years of age, or end of follow up (December 31st, 2006 in Sweden, December 31st, 2007 in Denmark), whichever came first. The 610 children who had both 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 minutes 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~~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 health care provider to report to the registers.[30~~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~~28~~]

Outcome measurements

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Data on cancer was obtained from national cancer registries, and the registration and coding practices have been described elsewhere.[31, 32~~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~~3~~, 4] leukemias (ICD-7 code 204, ICD-10 codes C91-95), lymphomas~~Hodgkin's lymphoma~~ (ICD-7 code 201-203, ICD-10 code C81-C85), brain and nervous system tumors (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' tumor (ICD-7 code 180 and PAD 886, ICD-10 code C64.9), ~~non-Hodgkin's lymphoma (ICD-7 codes 200, 202, ICD-10 codes C82-83), H~~hepatoblastoma~~tumors~~ (ICD-7 code 155, ICD-10 code C22), malignant bone tumors (ICD-7 code 196, ICD-10 codes C40-C41), and t~~T~~esticular~~s~~ cancer (ICD-7 code 178, ICD-10 code C62)~~, , Wilm's tumor (ICD-7 code 180 and PAD 886, ICD-10 code C64.9), retinoblastoma of the eye (ICD-7 code 192 and PAD 436, ICD-10 code C69.2), and central nervous system (CNS) tumors (ICD-7 code 193, ICD-10 codes C70-71).~~

Statistical analysis

All data handling and statistical analyses were performed using SAS version 9.2 statistical software package (SAS Institute, Inc., Cary, North Carolina). The low Apgar score was categorized into each single score and also into 2 subgroups (0-5 and 6-8), as a very low score would be different from a score of over 5.[10~~10~~] Hazards ratios with 95% confidence intervals were estimated by Cox regression with the PHREG procedure. Potential confounders were included in the model, such as country (Denmark, Sweden), child sex (male, female) and birth characteristics ((parity (1, 2, ≥3), birth weight (<2500 g, 2500-3249 g, 3250-3999 g, and ≥4000 g), gestational age (<37 weeks and ≥37 weeks)), maternal factors ((age (≤26 years, 27-30 years, and ≥31years), education level (low: ≤9 years,

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middle:10-14 years, and high: ≥15 years) (available Swedish data from 1990,1995, 2000, and 2005, available annual Danish data from 1978-2006),[29-29], smoking during pregnancy (yes, no) (available 1991-2007 in Denmark and 1983-2006 in Sweden)).

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Analyses were also 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' tumor, hepatoblastoma, testicular cancer, and retinoblastoma to see how the overall effect would be driven by these 4 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 sub-cohorts where information on maternal smoking was available.

~~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 sub-cohorts where information on maternal smoking was available.~~

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RESULTS

The baseline characteristics of the study population (5,061,798 singletons) are shown in Table 1 according to the 3 subgroups of Apgar scores (0 to 5, 6-8, and 9-10). Low Apgar scores were comparable for most characteristics but more frequent ~~common~~ among ~~boys, first-born children,~~ children born preterm or with low birth weight~~, children born to mothers with lower education or to mothers who smoked during pregnancy~~.

A total of 8087~~697~~ children were diagnosed with cancer before 14 years of age (1.6~~7~~ per 1000 children). Table 2 presents that children with a score of 0 to 5 had a higher overall rate of childhood cancer (2.0~~3~~ per 1000) than those with a score of 6 to 8 (1~~2~~.7~~0~~ per 1000), and those with a score of 9 to 10 (1.6~~7~~ per 1000). Compared to children with a five-minute Apgar score of 9-10, children with a score of 0-5 had a 46~~50~~% increased risk of cancer before 14 years of age (adjusted Hazard ratio (HR) 1.46~~50~~, 95% confidence interval (CI) 1.15~~9~~-1.89~~89~~), but ~~not and~~ children with a score of 6-8 had no increased risk of cancer ~~had a 14% increased risk~~ (HR ~~-~~1.05~~14~~, 95% CI 0~~1~~.90~~2~~-1.1~~2~~8).

Table 3 shows that the HRs in children according to age at cancer diagnosis. For cancer diagnosed before 6 months of age, an~~with a low~~ Apgar score of 0-5 was associated with 6-fold overall risk (HR 6.04, 95% CI 3.73-9.76) and an Apgar ~~. For estimate for a~~ score of 6-8 was associated with a two-fold increase in risk (HR 2.17, ~~(~~95% CI 1.54-3.05)~~ere higher in almost all strata, according to country, child's sex and birth characteristics (birth weight, gestational age, and birth order), and maternal factors (age, education, and smoking status during pregnancy)~~. The most frequent diagnosed cancers during this period include tumors from brain/nervous system, endocrinal glands, kidney, and leukemia/lymphomas (data not shown).There were no statistically significant increased risks for cancer diagnosed after~~t age of~~ 6 months of age~~to 5 years and at age older than 5 years~~.

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Compared to children with an Apgar score of 9-10, children with a score of 0-5 had higher risks for several ~~main~~ childhood cancers (CNS tumors, retinoblastoma, hepatic tumors, bone tumors, and testicular tumors), 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'~~'~~ tumor (HR 4.33~~78~~, 95% CI 2.42~~79~~-~~78~~.73~~19~~).

When Wilms' tumor, 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, ~~And~~ the estimates for cancer diagnosed before 6 months were~~are~~ even slightly higher ~~-~~(data not shown) than those presented in Table 3~~, compared to those presented in Table 3~~. When we excluded cancers diagnosed during~~in~~ the ~~-~~first 6 months of life, ~~the effect of~~ a low Apgar score was not associated with increased ~~on~~ overall cancer risk or ~~was not significant and neither for~~ with CNS cancer~~ CNS and nervous system~~ (data not shown). E~~But the e~~stimates for other cancers, such as Wilms' tumor, remained essentially unchanged~~ did not change much~~ (data not shown).

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

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~~according to country, child's sex and birth characteristics (birth weight, gestational age, and birth order), and maternal factors (age, education, and smoking status during pregnancy) (data not shown).~~

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DISCUSSION

Children with a low 5-minute Apgar score, especially children with a score of 0 to 5, had a higher overall risk of childhood cancer that was diagnosed before 6 months of age. We also observed ~~and~~ higher risks for several main childhood cancers like ~~. The association was independent of country, child sex, child birth characteristics (birth weight, birth order, and gestational age), and maternal factors (age, education, and smoking during pregnancy). Similar associations were seen for most childhood cancers, albeit the estimate was only statistically significant for~~ Wilms' tumor. The associations were~~as~~ 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 leukemia and other lymphatic / hemapoietic malignancies.

The theory of 'developmental-origins of health and disease' proposes the importance of in utero environment for~~in~~ long-~~-~~term human health.[22, 23~~22, 23~~] We observed that children with a low ~~any~~ Apgar score ~~(between 0 and 8 at 5 minutes, and especially those with a score~~ between~~of~~ 0 to 5~~)~~, had a higher overall cancer risk than those with an optimal score (~~of~~ 9 or~~to~~ 10). The mechanism underlying this observation is, however, unclear. ~~It should be noted that the Apgar score is a sum of 5 signs (rating 0 to 2), which are not of equal value.~~[10, 13] A low Apgar score is a marker of a suboptimal fetal environment [20] or other~~the~~ factors that prevent the child from achieving a high score. From ~~, or a suboptimal fetal environment~~,[20~~20~~] ~~that may have~~ a programming perspective, i~~effect on the development of childhood cancer. I~~t 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. Tumors from brain/nervous system, endocrinal glands, kidney, and leukemia/lymphomas were among the most frequent diagnosed cancers during this

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period. This observation is in line with suggestions from previous studies that ~~While i~~in utero exposures to insulin-like growth factors,[8] estrogens,[33, 34~~33, 34~~] or infections[24, 35~~24, 35~~] may play a role for ~~have been proposed to explain~~ the relationships between ~~most of~~ other birth outcomes and many childhood cancers, or childhood cancer risk in general. A low Apgar score probably shares ~~the~~ etiology with ~~those~~ cancers initiated~~developed~~ in fetal~~us~~ life, and d~~. It should be noted that the Apgar score is a sum of 5 signs (rating 0 to 2), which are not of equal value.~~[10, 13] ~~D~~, ~~d~~ifferent biological pathways may operate for the association between ~~the~~ Apgar score and childhood cancers. For example, ~~It can also be hypothesized that~~ neonatal treatments related to low Apgar scores may increase the risk of some childhood cancers.[36, 37~~36, 37~~]

~~The observed associations between low Apgar scores and childhood cancer risk were not explained by the role of 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 cancer.[6-9] However, the elevated risks related to a low score were observed in almost all subgroups, not restricted to adverse birth outcomes. Furthermore, the associations were consistent according to country and maternal factors under investigation.~~

The best evidence for fetal origins of childhood cancer has been available for leukemia.[7, 8, 38~~6-8~~] O~~But o~~ur findings suggest that those observations may operate through the mechanisms that do not affect the Apgar score, and s~~. S~~imilar interpretations apply to other lymphatic / hemapoietic neoplasms~~,~~ ~~and CNS tumors~~. 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' tumor, which is in line with observations in two register-based studies (restricted to only

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girls in one of the studies)[39, 40~~38, 39~~] but not in another case-control study.[41~~40~~] Hypoxia, as indicated by a low score, may result in cell damage that subsequently leads to Wilms' tumor.[42, 43~~41, 42~~] Alternatively, neonatal treatments provided to neonates with a low Apgar score may also increase the risk of Wilms' tumor.[36, 37~~36, 37~~] Hepatoblastoma is reported to be associated with factors like low birth weight,[44~~43~~] smoking during pregnancy or young maternal age.[45~~44~~] A recent study showed a reverse association between birth order and retinoblastoma.[9~~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 ~~the role of~~ 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~~ed~~ 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 ~~singletons in a~~ prospective~~ly~~ longitudinal design, ~~,~~ large sample size, ~~complete follow up,~~ 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 ~~both~~ factors related to the child or~~and~~ the mother. Our data enabled us to do a more in-depth investigation

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by examining ~~the~~ risks in subgroups. The cohort design based on prospectively collected high quality data minimized the impact of information ~~bias~~ or recall bias. ~~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~~27~~]

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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~~45~~] ~~–~~A s~~S~~econd limitation is that we cannot rule out the confounding of factors like environmental exposures after birth. Third~~ly~~, the case numbers for several childhood cancers are small, although the total population included over 5 million children.

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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 ~~it will further~~ strengthens the relevance of viewing the prenatal time period as a causal time window of interest. A low Apgar score may reflect a pathologic pregnancy which 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.

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Competing Interests None.

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.

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.

Data sharing statement There are no additional data available.

ARTICLE SUMMARY

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Article focus

- The etiology 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 five-minute 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 minutes 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 5 million, complete follow up, accurate data on Apgar score ~~exposure~~ and cancer diagnosis~~outcome~~, 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.

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

Variables	Apgar score at 5 minutes			
	0-5	6-8	9-10	Unknown
Country				
Denmark	10,6737 (132)	42,11851 (27)	1,669,95670,475 (936)	189,86874 (18)
Sweden	22,6948 (168)	116,1677 (473)	2,951,0693 (9064)	229,64953 (792)
Sex				
Boys	18,82934 (156)	8990,97003 (357)	2,3656,951258 (951)	126,0114 (51)
Girls	14,53740 (144)	68,3125 (43)	2,255,068310 (9249)	122,50613 (549)
Birth order				
1	16,9105 (51)	91,199222 (458)	1,971,064289 (9043)	100,23942 (540)
2	93889 (128)	42,29300 (27)	1,6945,866084 (9237)	93,2328 (538)
≥3	57823 (17)	23,09119 (215)	89984,631716 (9219)	4848,4047 (519)
Unknown	12878 (24)	17057 (21)	60,45879 (861)	6646 (93)
Gestational age				

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<37 weeks	89023 (427)	27,3348 (117)	191,5287 (794)	14,43941 (6)
>=37 weeks	22,9907 (<169)	129,23870 (382)	4,368,046538 (925)	226,66876 (591)
Unknown	1475 (24)	17109 (21)	61,42143 (851)	7410 (103)
Birth weight (g)				
<2500	823840 (25)	22,4895 (134)	135,895925 (763)	11,1502 (64)
2500-3249	7766 (123)	39,82438 (325)	1,137,398533 (9125)	62,399402 (25)
3250-3999	10,9948 (<133)	65,66983 (241)	2,448,691948 (9253)	128,2679 (52)
>=4000	43401 (<113)	27,73642 (318)	833,472578 (9218)	37,4979 (415)
Unknown	202930 (36)	256770 (32)	65,56384 (831)	92045 (124)
Maternal age				
<=26	12,9369 (139)	60,05166 (38)	1,690,721935 (9037)	120,96974 (649)
27-30	92935 (128)	45,16274 (329)	1,378,031188 (9230)	68,4910 (528)
≥31	11,1347 (133)	53,06076 (34)	1,552,18002 (9334)	59,00923 (24)
Unknown	4 (<1)	12 (4<1)	265 (83<1)	39 (12<1)

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Maternal education (years)				
Low (≤9)	16,3469 (149)	72,58398 (346)	2,006,475645 (9043)	146,2207 (759)
Middle (10-14)	87705 (126)	45,00718 (328)	1,2967,875059 (928)	52,0457 (421)
High (≥15)	5600 (17)	28,1230 (318)	908,327454 (9320)	36,363 (415)
Unknown	2651 (18)	12,57582 (38)	409,342410 (93)	13,88990 (36)
Maternal smoking during pregnancy†				
Yes	47556 (122)	21,25460 (318)	633,618236 (194)	10,9357 (21)
No	14,66617 (612)	85,12230 (73)	2,419,740935 (9574)	32,3035 (61)
Unknown	23985 (11)	95147 (48)	222,589604 (917)	9968 (419)

* Value is n (%). Study population includes all 5,0961,18798 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.

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Table 2. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes.

Apgar score	Cases (rate per 1000)	Crude HR	Adjusted HR (95%CI) *
0	3 (0.7)	0.474 (0.154-1.4536)‡	0.5647 (0.185-1.7345)‡
1	15 (2.9)	2.4428 (1.4738-43.0478) ‡‡	2.1720 (1.312-3.6805)‡‡
2	67 (1.923)	1.8947 (0.61-3.54)	1.7244 (0.7760-3.8245)
3	911 (2.16)	1.852.13 (0.961.18-3.5684)‡	1.672.06 (01.8714-3.2172)‡
4	14 (2.2)	1.6152 (0.9488-2.7861)	1.4848 (0.866-2.5554)
5	216 (2.15)	1.4065 (01.9111-2.1844) ‡	1.3262 (01.8510-2.0540)‡
0-5 combined	***6876 (2.03)***	***1.547 (1.215-1.968)-‡‡***	***1.4656 (1.1523-1.8996)-‡‡***
6	2834 (1.58)	1.0317 (0.7184-1.4964)	01.95.15 (0.6682-1.3834)
7	617 (1.68)	1.1507 (0.9984-1.347)	1.005 (0.7782-1.2934)

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8	177208 (1.72-1)	1.1826 (1.0810-1.2945)‡	1.0823 (01.9307-1.2642)‡
6-8 combined	***266309 (1.72-0)***	***1.1221 (0.991.07-1.2735)‡***	***1.0518 (01.9205-1.1832)***
9-10	***7216765 (1.67)***	***1.0 (ref)***	***1.0 (ref)***

* Adjusted for country, sex, and maternal factors at child birth (age, education, and smoking during pregnancy).

‡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, birth order).

†‡ P<0.05.

Table 3. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes, by age at diagnosis.

Age at diagnosis	The Apgar score	Cases (rate, ‰)	Crude HR (95%CI)	Adjusted HR (95%CI)*
Under 6 months				
	0-5	20 (0.6)	6.65 (4.15-10.65) †	6.04 (3.73-9.76) †
	6-8	39 (0.2)	2.43 (1.73-3.39) †	2.17 (1.54-3.05) †
	9-10	465 (0.1)	1.0 (ref)	1.0 (ref)
6 months-5 years				
	0-5	25 (0.9)	1.21 (0.82-1.79)	1.18 (0.80-1.76)

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	6-8	134 (0.9)	1.15 (0.97-1.36)	1.09 (0.92-1.30)
	9-10	3678 (0.8)	1.0 (ref)	1.0 (ref)
> 5 years				
	0-5	23 (1.0)	1.17 (0.78-1.77)	1.10 (0.73-1.65)
	6-8	93(0.7)	0.89 (0.73-1.10)	0.83 (0.67-1.02)
	9-10	3223 (0.8)	1.0 (ref)	1.0 (ref)

*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).

† P<0.05.

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Table 3. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes, stratified on country, birth characteristics and maternal variables.

Variable		Apgar score	Cancer cases (rate, per 1000)	Crude HR* (95%CI)	Adjusted HR‡ (95%CI)
Country	Denmark	1-5	20 (1.9)	1.57 (1.25-1.98)‡	1.52 (1.23-1.91)‡
		6-8	72 (1.7)	1.21 (1.07-1.35)‡	1.16 (1.03-1.30)‡
		9-10	2461 (1.5)	1.0 (ref)	1.0 (ref)
	Sweden	1-5	56 (2.5)	1.65 (1.26-2.15)‡	1.60 (1.23-2.09)‡
		6-8	237 (2.0)	1.26 (1.06-1.38)‡	1.16 (1.02-1.33)‡
		9-10	5304 (1.8)	1.0 (ref)	1.0 (ref)
Sex	Male	1-5	44 (2.6)	1.54 (1.13-2.08)‡	1.46 (1.07-1.99)‡
		6-8	169 (1.9)	1.09 (0.94-1.28)	1.04 (0.89-1.22)
		9-10	4232 (1.8)	1.0 (ref)	1.0 (ref)
	Female	1-5	32 (2.5)	1.60 (1.12-2.29)‡	1.55 (1.08-2.23)‡
		6-8	140 (2.0)	1.35 (1.14-1.60)‡	1.29 (1.09-1.53)‡
		9-10	3533 (1.6)	1.0 (ref)	1.0 (ref)
Birth order	1	1-5	38 (2.5)	1.45 (1.04-2.02)‡	1.38 (0.99-1.93)

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		6-8	174 (2.0)	1.14 (0.98-1.33)	1.10 (0.94-1.28)
		9-10	3385 (1.6)	1.0 (ref)	1.0 (ref)
	2	1-5	16 (1.7)	1.28 (0.78-2.09)	1.18 (0.72-1.93)
		6-8	72 (1.7)	1.08 (0.85-1.36)	0.99 (0.78-1.26)
		9-10	2797 (1.7)	1.0 (ref)	1.0 (ref)
	3	1-5	16 (2.8)	2.11 (1.29-3.46)‡	2.13 (1.29-3.49)‡
		6-8	59 (2.6)	1.63 (1.26-2.12)‡	1.60 (1.23-2.09)‡
		9-10	1480 (1.7)	1.0 (ref)	1.0 (ref)
Gestational age	<37 weeks	1-5	17 (1.9)	1.53 (1.16-2.00)‡	1.48 (1.13-1.94)‡
		6-8	63 (2.6)	1.16 (1.02-1.32)‡	1.12 (0.99-1.28)
		9-10	353 (1.8)	1.0 (ref)	1.0 (ref)
	≥37 weeks	1-5	57 (2.5)	1.74 (1.07-2.84)‡	1.71 (1.04-2.79)‡
		6-8	244 (1.9)	1.34 (1.02-1.75)‡	1.30 (0.99-1.71)
		9-10	7304 (1.7)	1.0 (ref)	1.0 (ref)
Birth weight	<2500 g	1-5	13 (1.6)	1.65 (0.94-2.88)	1.52 (0.86-2.66)
		6-8	46 (2.0)	1.32 (0.96-1.81)	1.20 (0.87-1.65)
		9-10	235 (1.7)	1.0 (ref)	1.0 (ref)

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	2500-3249g	1-5	18 (2.3)	1.54 (0.95-2.48)	1.50 (0.93-2.41)
		6-8	88 (2.2)	1.39 (1.12-1.73)‡	1.33 (1.07-1.66)‡
		9-10	1802 (1.6)	1.0 (ref)	1.0 (ref)
	3250-3999g	1-5	28 (2.5)	1.56 (1.07-2.28)‡	1.51 (1.04-2.21)‡
		6-8	126 (1.9)	1.20 (1.00-1.43)‡	1.15 (0.96-1.37)
		9-10	4079 (1.7)	1.0 (ref)	1.0 (ref)
	≥4000 g	1-5	10 (2.3)	1.22 (0.63-2.34)	1.18 (0.61-2.26)
		6-8	44 (1.6)	0.89 (0.66-1.20)	0.86 (0.63-1.16)
		9-10	1536 (1.8)	1.0 (ref)	1.0 (ref)
Maternal age	<=26	1-5	30 (2.3)	1.50 (1.04-2.18)‡	1.42 (0.98-2.06)
		6-8	114(1.9)	1.09 (0.90-1.31)	1.03 (0.85-1.25)
		9-10	3051 (1.8)	1.0 (ref)	1.0 (ref)
	27-30	1-5	24 (2.6)	1.73 (1.14-2.64)‡	1.73 (1.13-2.63)‡
		6-8	101(2.2)	1.42 (1.16-1.73)‡	1.39 (1.13-1.70)‡
		9-10	2271 (1.6)	1.0 (ref)	1.0 (ref)
	≥31	1-5	22 (2.0)	1.53 (1.01-2.33)‡	1.42 (0.93-2.17)
		6-8	94 (1.8)	1.17 (0.95-1.44)	1.08 (0.87-1.33)

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		9-10	2443 (1.6)	1.0 (ref)	1.0 (ref)
Maternal education	Low	1-5	43 (2.6)	1.77 (1.30-2.39)‡	1.67 (1.23-2.27)‡
		6-8	164 (2.3)	1.27 (1.08-1.49)‡	1.20 (1.03-1.41)‡
		9-10	3692 (1.8)	1.0 (ref)	1.0 (ref)
	Middle	1-5	17 (1.9)	1.30 (0.80-2.13)	1.25 (0.76-2.06)
		6-8	62 (1.4)	0.88 (0.68-1.13)	0.84 (0.65-1.08)
		9-10	2155 (1.7)	1.0 (ref)	1.0 (ref)
	High	1-5	8 (1.4)	1.57 (1.22-2.02)‡	1.48 (1.15-1.92)‡
		6-8	64 (2.3)	0.97 (0.46-2.04)	0.95 (0.45-2.01)
		9-10	1357 (1.5)	1.0 (ref)	1.0 (ref)
Maternal smoking	Yes	1-5	6 (1.3)	0.89 (0.40-1.99)	0.86 (0.38-1.92)
		6-8	48 (2.3)	1.36 (1.02-1.82)‡	1.28 (0.96-1.72)
		9-10	1074 (1.7)	1.0 (ref)	1.0 (ref)
	No	1-5	40 (2.7)	2.10 (1.53-2.88)‡	2.07 (1.51-2.85)‡
		6-8	144 (1.7)	1.17 (0.99-1.38)	1.10 (0.93-1.30)
		9-10	3629 (1.5)	1.0 (ref)	1.0 (ref)

*Crude analysis.

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~~‡Adjusted for country, sex, maternal factors (age, education, and smoking during pregnancy), and birth characteristics of the child (birth weight, gestational age, and birth order).~~

~~‡ P<0.05.~~

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Table 4. Hazard Ratios (HRs) for main childhood cancers according to the Apgar score at 5 minutes

Cancer type	Apgar score	Cancer cases (rate per 1000)	Crude HR (95% CI)	Adjusted HR[‡*] (95% CI)
Leukemia	0-5	13 (0.4)	1~~0~~.0~~9~~3 (0.6054-1.7964)	1~~0~~.0598 (0.6157-1.8169)
	6-8	7185 (0.5)	1.0213 (0.891-1.2941)[‡]	1.0215 (0.8093-1.2943)
	9-10	2122~~3~~14 (0.5)	1.0 (ref)	1.0 (ref)
~~**Hodgkin's disease**~~	~~0-5~~	~~0 (-)~~	-	-
	~~6-8~~	~~2(<0.05)~~	~~0.49 (0.12-1.99)~~	~~0.42 (0.10-1.71)~~
	~~9-10~~	~~126 (<0.05)~~	~~1.0 (ref)~~	~~1.0 (ref)~~
Lymphomas~~**Non-Hodgkin's disease**~~	0-5	3 (0.1)	0~~1~~.8~~4~~12 (0.2736-2~~3~~.6049)	0.~~9~~73 (0.231-2~~3~~.~~0~~27)
	6-8	1~~2~~0 (0.1)	0.6~~2~~9 (0.357-1.0~~2~~9)	0.5~~1~~5 (0.29-0~~1~~.9~~0~~03)
	9-10	598~~449~~ (0.1)	1.0 (ref)	1.0 (ref)
CNS cancers	0-5	21~~20~~ (0.~~6~~6)	1.2~~4~~2 (0.7~~8~~6-	1.22~~1~~8 (0.7~~7~~3-1.9~~4~~0)

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			1.9896)	
	6-8	104104 (0.77)	1.2934 (1.106-1.5763)‡‡	1.269 (1.036-1.548)‡‡
	9-10	243245 (0.5)	1.0 (ref)	1.0 (ref)
Retinoblastoma	0-5	3 (0.1)	2.2001 (0.7064-6.8427)	2.0385 (0.6459-6.3980)
	6-8	49 (<0.051)	01.5207 (0.1955-12.3907)	0.4899 (0.1850-1.2893)
	9-10	24063 (0.1)	1.0 (ref)	1.0 (ref)
Wilms'' tumor	0-5	124 (0.4)	4.6298 (2.6193-8.2047)‡‡	4.3378 (2.4279-78.7319)‡‡
	6-8	1820 (0.1)	1.247 (0.7781-1.99)	1.1622 (0.728-1.8791)
	9-10	4484 (0.1)	1.0 (ref)	1.0 (ref)
Hepatoblastoma	0-5	12 (<0.051)	13.7824 (0.2580-123.7612)	12.5164 (0.2165-10.986)
	6-8	45 (<0.05)	1.2744 (0.4759-	1.0622 (0.349-

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			3.4~~4~~53)	2~~3~~.9~~0~~2)
	9-10	96~~10~~7 (<0.05)	1.0 (ref)	1.0 (ref)
Bone cancer	0-5	3 (0.1)	2.25~~0~~0 (0.72~~6~~4-7~~6~~.02~~3~~)	2~~1~~.05~~8~~7 (0.65~~0~~-6~~5~~.45~~8~~8)
	6-8	6~~7~~ (<0.05)	0.85~~8~~ (0.38~~4~~1-1.90~~8~~6)	0.79~~8~~5 (0.35~~4~~0-1.80~~2~~)
	9-10	220~~4~~8 (0.1)	1.0 (ref)	1.0 (ref)
Testicular cancer	0-5	0 (0)	-	-
	6-8	4~~5~~ (<0.05)	2.08~~4~~4 (0.76~~9~~8-5~~6~~.0~~7~~5)	1~~2~~.89~~1~~5 (0.68~~6~~-5.42~~5~~)
	9-10	59~~6~~4 (<0.05)	1.0 (ref)	1.0 (ref)

* 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, birth order).

† P<0.05.

~~* Adjusted for country, sex, and maternal factors at child birth (age, education, and smoking during pregnancy).~~

~~‡ Adjusted for country, sex, and maternal factors at child birth (age, education, and smoking during pregnancy), and birth characteristics of the child (birth weight, gestational age, and birth order).~~

~~‡ P<0.05.~~

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4,5*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	4

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15,16
		(b) Indicate number of participants with missing data for each variable of interest	15,16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	15,16
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 15-25
		(*b*) Report category boundaries when continuous variables were categorized	6,15-25
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6,15-25
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15-25
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9,10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.