PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Five-minute Apgar Score as a Predictor of Childhood Cancer: a population-based Cohort Study in Five Million Children
AUTHORS	Li, Jiong ; Cnattingius, Sven; Gissler, M; VESTERGAARD, Mogens; Obel, Carsten; AHRENSBERG, Jette; Olsen, Jørn

VERSION 1 - REVIEW

REVIEWER	Logan G. Spector Associate Professor Division of Epidemiology/Clinical Research Department of Pediatrics University of Minnesota Minneapolis, Minnesota USA I have no competing interests to declare.
REVIEW RETURNED	02-May-2012

THE STUDY	I don't believe the authors have adequately described alternate explanations for why cancer risk is higher with lower apgar score. For instance, they neglected to mention birth defects - which have frequently been associated with childhood cancers and are also a cause of distress at birth.
RESULTS & CONCLUSIONS	Regarding the presentation- it is mostly well-presented, but there are a few outstanding issues. For one, in Table 1 percentages should be presented in rows rather than columns (e.g. the % of subjects in each apgar category within Denmark or Sweden). Table 2 presents two sets of adjusted HR's, but there is no rational given for the adjustment without birth weight/gestational age (left column). Also, the footnote indicates $p< 0.05$ for numerous HR's where the confidence interval includes 1. Table 3 presents HRs stratifed by a number of factors, which implies interaction, however no p-value for interaction is presented. A larger point (viz. Table 4) is that it is surprising that the HRs for overall cancer are elevated and significant given the null associations for leukemia and lymphoma, which comprise nearly half of childhood cancer cases. How much of the overall results are driven by Wilm's tumor or other individual tumors? The authors should repeat the overall analyses dropping Willm's tumor and other classes of tumor with elevated HRs in turn to see the effect. It's also well-known that embryonal cancers initiate in utero and may be quite developed at birth. Can the authors repeat analyses excluding cancers diagnosed in the first few months of life (say 6)?

REVIEWER	Susan E. Carozza, PhD

	Associate Professor School of Biological & Population Health Sciences College of Public Health & Human Sciences Oregon State University Corvallis, OR USA I have no competing interests in regards to this manuscript.
REVIEW RETURNED	02-May-2012

RESULTS & CONCLUSIONS	Table 1 would better support the Result text if percentages were presented by row rather than column.
GENERAL COMMENTS	This is an interesting analysis and adds to the body of work around prenatal exposures and childhood cancers. It would be more easily interpreted and compared with other studies, however, if the authors had used the conventional cancer groupings of the International Classification of Childhood Cancer (ICCC-3). This site/histology recode system better captures the types of cancers seen in children, which are quite different from those typically diagnosed in adults, and it is a more comprehensive approach. One other aspect that might be interesting to investigate with these data is the association of Apgar score with age at diagnosis - it might be that any effect is confined to children diagnosed with cancer before age 5, for instance.

VERSION 1 – AUTHOR RESPONSE

----------Reviewer 1: Susan E. Carozza, PhD
Comment 1: Table 1 would better support the Result text if percentages were presented by row rather than column.

Response: Table 1 was revised as suggested.

Comment 2: This is an interesting analysis and adds to the body of work around prenatal exposures and childhood cancers. It would be more easily interpreted and compared with other studies, however, if the authors had used the conventional cancer groupings of the International Classification of Childhood Cancer (ICCC-3). This site/histology recode system better captures the types of cancers seen in children, which are quite different from those typically diagnosed in adults, and it is a more comprehensive approach. One other aspect that might be interesting to investigate with these data is the association of Apgar score with age at diagnosis - it might be that any effect is confined to children diagnosed with cancer before age 5, for instance.

Response:
Unfortunately the Danish and Swedish cancer registers used the ICD-7 and ICD-10 system. It is difficult to covert the two ICD coding systems, especially the ICD-7 codes, into the exact same ICCC diagnostic groups, giving the changes over decades. However, we tried to group the cases according to the 12-ICCC diagnostic groups, and we now have first 8 main groups: leukemias (I), lymphomas (II), brain and nervous systems codes (III and IV), retinoblastoma (V), renal tumors (VI, Wilms tumor), hepatic tumors (VII), and malignant bone tumors (VIII), as well as testicular cancer, which have been proposed to have a prenatal origin. We believe that we have captured most of the childhood cancers using this method.

The age at diagnosis was taken into consideration in this revised version (Methods section: page 6,

paragraph 1). The results show that the effect of a low Apgar score on overall cancer risk was mainly confined to children diagnosed shortly after birth, although the risks for the several specific cancers remained increased (Results section: page 7; Tables 3, 4). We have incorporated this in discussion (Page 9, paragraph 2).

----------Reviewer 2: Logan G. Spector
Comment 1: I don't believe the authors have adequately described alternate explanations for why cancer risk is higher with lower apgar score. For instance, they neglected to mention birth defects - which have frequently been associated with childhood cancers and are also a cause of distress at birth.

Response:
Interpretation of the observed associations is still open to discussion and further research is needed to explore the specific underlying pathways (Page 9, paragraph 2).
Birth defect is an important issue and we now excluded all those children who received a cancer diagnosis and had birth defects (Methods section: page 4, paragraph 1). The overall effect of a low score did not change much (Tables 2-4), compared to estimates when these children were included (data not shown).

Comment 2: Regarding the presentation- it is mostly well-presented, but there are a few outstanding issues. For one, in Table 1 percentages should be presented in rows rather than columns (e.g. the % of subjects in each apgar category within Denmark or Sweden). Table 2 presents two sets of adjusted HR's, but there is no rational given for the adjustment without birth weight/gestational age (left column). Also, the footnote indicates p< 0.05 for numerous HR's where the confidence interval includes 1. Table 3 presents HRs stratifed by a number of factors, which implies interaction, however no p-value for interaction is presented.
Response:
Table 1 is revised as suggested, and the results for first model are left out. The typos for P<0.05 are corrected. Because the main issue of this study aimed to examine the associations between Apgar score and cancer risk, we left out previous table 3 for subgroup analyses according to covariates, for which the results were only described in text (Method section: page 8, paragraph 3).

Comment 3: A larger point (viz. Table 4) is that it is surprising that the HRs for overall cancer are elevated and significant given the null associations for leukemia and lymphoma, which comprise nearly half of childhood cancer cases. How much of the overall results are driven by Wilm's tumor or other individual tumors? The authors should repeat the overall analyses dropping Willm's tumor and other classes of tumor with elevated HRs in turn to see the effect.
Response:
When we repeated overall analyses by dropping Wilms tumor, testicular cancer, hepatic cancer, and retinoblastoma, the estimates for overall effect are smaller but the risk remains elevated, as shown in Table 2-1 here. And the estimates for cancer diagnosed before 6 months are even slightly higher (Table 3-1), compared to those presented in the manuscript (Table 3).

Table 2-1. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes*

Score	Cases (rate ‰)	Crude HR	Adjusted HR
0	2 (0.4)	0.42 (0.10-1.68)	0.35 (0.09-1.40)
1	14 (2.7)	2.30 (1.36-3.89)	2.55 (1.51-4.32) †
2	4 (1.3)	1.30 (0.49-3.47)	1.42 (0.53-3.79)
3	6 (1.4)	1.26 (0.57-2.82)	1.40 (0.63-3.11)
4	8 (1.3)	0.91 (0.45-1.90)	0.99 (0.47-2.07)
5	18 (1.8)	1.28 (0.79-2.05)	1.35 (0.84-2.18)

0-5 combined 52 (1.6) 1.32 (1.00-1.74) † 1.26 (0.95-1.66)
6 24 (1.3) 0.93 (0.62-1.39) 1.00 (0.67-1.50)
7 55 (1.5) 1.02 (0.78-1.34) 1.09 (0.84-1.43)
8 157 (1.5) 1.09 (0.93-1.27) 1.16 (0.99-1.36)
6-8 combined 236 (1.5) 1.13 (0.99-1.28) 1.06 (0.93-1.20)
9-10 6377 (1.4) 1.0 (ref) 1.0 (ref)
*Excluded cancer cases of Wilms' tumor, testicular cancer, hepatic cancer, and retinoblastoma.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 3-1. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes, by age at diagnosis.
Age Score Cases (‰) Crude HR Adjusted HR
< 6 mths
0-5 19 (0.6) 7.94 (4.89-12.93) † 7.09 (4.31-11.67) †
6-8 36 (0.2) 2.83 (1.99-4.02) † 2.49 (1.74-3.56) †
9-10 369 (0.1) 1.0 (ref) 1.0 (ref)
6 mths-5 years
0-5 15 (0.6) 0.88 (0.53-1.46) 0.87 (0.52-1.44)
6-8 115 (0.8) 1.18 (0.99-1.44) 1.14 (0.94-1.38)
9-10 2920 (0.6) 1.0 (ref) 1.0 (ref)
> 5 years
0-5 18 (1.0) 0.96 (0.60-1.53) 0.90 (0.57-1.44)
6-8 85(0.7) 0.86 (0.69-1.06) 0.79 (0.64-0.99)
9-10 3088 (0.8) 1.0 (ref) 1.0 (ref)
*Excluded cancer cases of Wilms tumor, testicular cancer, hepatic cancer, and retinoblastoma.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.

Comment 4: It's also well-known that embryonal cancers initiate in utero and may be quite developed at birth. Can the authors repeat analyses excluding cancers diagnosed in the first few months of life (say 6)?

Response:
We thank the reviewer for this sensible comment. The most frequent cancers diagnosed before 6 months are tumors from brain/nervous system, endocrinal glands, kidney, and leukemia/lymphomas. It is interesting to observe that the overall effect of a low Apgar score was confined to children diagnosed before age of 6 months, suggesting that a low Apgar scores and cancers developed in fetal life may share risk factors. We have incorporated this in discussion (Page 9, paragraph 2).

When we exclude cancers diagnosed during the first 6 months of life, the overall effect of a low Apgar score was not significant (Tables 2-2, 2-3). As expected, the risks of embryonal cancers were reduced or disappeared, but for other cancers (like Wilms' tumor), the estimates did not change much (Table 4-2).

Table 2-2. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes (exclude cancers diagnosed in first 6 months of life).

Apgar score	Cases (rate, ‰)	Crude HR	Adjusted HR†
0	3 (0.7)	0.50 (0.16-1.53)	0.59 (0.19-1.83)
1	8 (1.6)	1.37 (0.69-2.75)	1.23 (0.62-2.47)
2	4 (1.3)	1.34 (0.50-3.58)	1.23 (0.46-3.29)
3	8(1.9)	1.76 (0.88-3.52)	1.60 (0.80-3.20)
4	10(1.6)	1.33 (0.71-2.47)	1.23 (0.66-2.28)
5	15 (1.5)	1.13 (0.68-1.87)	1.06 (0.64-1.77)
0-5 combined			
	48 (1.4)	1.19 (0.89-1.58)	1.14 (0.86-1.52)
6	23 (1.2)	0.91 (0.61-1.36)	1.06 (0.80-3.20)
7	54 (1.4)	1.03 (0.79-1.35)	0.97 (0.74-1.26)
8	150 (1.5)	1.05 (0.89-1.24)	0.99 (0.84-1.16)
6-8 combined			
	227 (1.4)	1.03 (0.90-1.18)	0.97 (0.85-1.10)
9-10	6751 (1.5)	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.

Table 3-2. Hazard Ratios (HRs) for childhood cancer according to the Apgar score at 5 minutes, by age at diagnosis (exclude cancers diagnosed in first 6 months of life).

Age	Score	Cases (‰)	Crude HR	Adjusted HR
Under 6 mths	-	-	-	
6 mths-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 (0.97-1.37)	1.09 (0.92-1.30)
	9-10	3528 (0.8)	1.0 (ref)	1.0 (ref)
> 5 years				
	0-5	23 (1.0)	1.17 (0.78-1.77)	1.10 (0.67-1.65)
	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, birth order). † P<0.05.

Table 4-2. Hazard Ratios (HRs) for main childhood cancers according to the Apgar score at 5 minutes (exclude cancers diagnosed in first 6 months of life).

Cancer	Score	Cases (rate, ‰)	Crude HR	Adjusted HR
Leukemia	0-5	10 (0.3)	0.81 (0.43-1.50)	0.82 (0.44-1.52)
	6-8	68 (0.5)	1.00 (0.78-1.27)	0.99 (0.77-1.26)
	9-10	2083 (0.5)	1.0 (ref)	1.0 (ref)
Lymphomas	0-5	2 (0.1)	0.61 (0.15-2.45)	0.52 (0.13-2.07)
	6-8	12 (0.1)	0.68 (0.38-1.20)	0.55 (0.31-0.98)
	9-10	545 (0.1)	1.0 (ref)	1.0 (ref)
CNS /nervous system cancers				
	0-5	14 (0.4)	0.95 (0.55-1.65)	0.94 (0.55-1.63)
	6-8	87 (0.5)	1.16 (0.93-1.44)	1.14 (0.92-1.42)
	9-10	2102 (0.5)	1.0 (ref)	1.0 (ref)

Retinblastoma 0-5 3 (<0.05) 2.72 (0.87-8.52) 2.42 (0.77-7.63)
6-8 3 (<0.05) 0.49 (0.15-1.51) 0.43 (0.14-1.35)
9-10 194 (<0.05) 1.0 (ref) 1.0 (ref)
Wilms' tumor 0-5 11 (0.3) 4.51 (2.48-8.21) † 4.23 (2.31-7.25) †
6-8 18 (0.1) 1.32 (0.82-2.12) 1.24 (0.77-2.00)
9-10 417 (0.1) 1.0 (ref) 1.0 (ref)
Hepatoblastoma 0-5 1 (<0.05) 2.14 (0.30-15.38) 1.79 (0.25-13.05)
6-8 3 (<0.05) 1.15 (0.36-3.63) 0.97 (0.30-3.09)
9-10 80 (<0.05) 1.0 (ref) 1.0 (ref)
Bone cancer 0-5 2 (<0.05) 1.54 (0.38-6.21) 1.49 (0.37-6.02)
6-8 4 (<0.05) 0.58 (0.22-1.56) 0.56 (0.21-1.51)
9-10 214 (0.1) 1.0 (ref) 1.0 (ref)
Testicular cancer 0-5 0 (0) - -
6-8 3 (<0.05) 1.79 (0.56-5.23) 1.61 (0.50-5.20)
9-10 52 (<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.

VERSION 2 – REVIEW

REVIEWER	Logan G. Spector Associate Professor Division of Epidemiology/Clinical Research Department of Pediatrics University of Minnesota Minneapolis, MN USA
REVIEW RETURNED	29-Jun-2012

- The reviewer completed the checklist but made no further comments.