Author's response to reviews

Title: Apgar score and hospitalization for epilepsy in childhood

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Author's response to reviews: see over
Dear Editor,

Thank you very much for the opportunity to revise our manuscript for possible publication in BMC Public Health. We would like to thank Dr. Dunn and Dr. Sheiner for the time taken to review the manuscript and for their very helpful comments. Below we detail the changes made in the manuscript in response to the reviewers’ comments. We hope that you find our manuscript suitable for publication and look forward to learning about your decision.

Sincerely,

Vera Ehrenstein
Corresponding author
Reviewer 1: Dr. David W Dunn
Reviewer's report:

General
I think the reader might better appreciate the information in this report if the author gave an explanation of what definition of epilepsy was used. It appears that the discharge diagnosis was used for the first part of the study and a more exacting definition was used for validation of the diagnosis in a subsample of 69 children. Do they define epilepsy as two or more unprovoked seizures or one seizure with pathognomonic changes on EEG? Were febrile seizures excluded?

We added a reference for epilepsy classification used in Denmark and modified the pertinent paragraph in the RESULTS to read (pages 5-6) as follows:

For 69 randomly selected children hospitalized with epilepsy in 1998-2000, we compared Hospital Discharge Registry records with paper medical records in order to estimate positive predictive value of the registered discharge diagnosis. For chart records, we defined an epilepsy case as a physician-recorded epilepsy diagnosis, based on two or more unprovoked seizure episodes or on EEG findings, or both [21]. Febrile seizures were excluded.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)

1. Title, abstract, and introduction seem acceptable. The question is good. There is disagreement about the value of the Apgar score and seizures are a common problem in childhood.

2. Sample: As stated under general comments, there is a question about the meaning of "epilepsy".

Please see our response above, under ‘General’.

3. Data analysis: Does "birth defect" refer to malformations noted at the time of birth, or to malformations discovered at any time during life?

In the first paragraph of the METHODS, we defined the birth defects variable more precisely (page 4):

In the Birth Registry, we identified all single live births from 1978 through 2001 and retrieved variables for five-minute Apgar score, birth weight, gestational age, mode of delivery, birth presentation, birth defects (defined here as malformations
discovered during the birth hospitalization), mother’s age, and mother’s smoking in pregnancy.

4. Results: Are the 1079 infants with missing 5-minute Apgar any different from the remainder of the sample? Could it be that Apgar scores were more often overlooked in severely ill infants requiring resuscitation?

In response to this comment, we added the following paragraph to the RESULTS (page 8):

Compared with the analysis cohort, the small (<1%) group of infants with a missing 5-minute Apgar score had a lower median birth weight, higher prevalence of birth defects, and were more likely to be in a non-cephalic birth presentation. The risk of epilepsy among them was 0.6 percent (6 cases). Under the hypothetical extreme assumption that all these newborns actually had a 5-minute Apgar score below 7, the 12-year risk of epilepsy hospitalisation in the exposed group would have decreased slightly but would still be about twice the risk among infants with Apgar score of 7 or greater. Such an extreme distribution of missing Apgar score values would of course be unlikely, given their observed distribution in the analysis cohort and median follow-up time of 12 years.

5. Results: The authors note that 25% of records had incorrect diagnosis. In the discussion they assume the rate of false diagnosis would not differ by Apgar score. However, is it possible that the children with a seizure but not epilepsy, asphyxia, mental retardation, unspecified neurological problems, and heart failure may have been more likely to have a lower Apgar? What were the Apgar cores for the 17 unconfirmed cases?

In response to this comment, we added the following sentence to the paragraph dedicated to the results of validation (page 8):

Five-minute Apgar scores for all children with unconfirmed diagnoses were above six.
Reviewer 2. Dr. Eyal Sheiner
Reviewer's report:

General
This is a large epidemiological study, including an impressive cohort of over 130,000 deliveries in Denmark. The study is interesting and well written. Obviously, it has several important limitations, and the authors have discussed most of them in the discussion section. I have several comments to the authors.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Abstract: please add what other perinatal risk factors were adjusted for.

The last sentence of the Methods section in the ABSTRACT now reads:

We adjusted risk ratio estimates for birth weight, gestational age, mode of delivery, birth presentation, mother’s age at delivery, and birth defects.

2. Methods: This reviewer is not familiar with “manual” delivery. I assume the authors mean vacuum delivery, and it should be corrected.

In response to this comment, we changed the relevant paragraph on page 5 as follows:

We used Poisson regression [19, 20] to model the rate of epilepsy hospitalization and to estimate the risk ratio, while adjusting simultaneously for the effects of non-cephalic birth presentation, birth weight, gestational age, maternal age, birth defects, and mode of delivery (spontaneous, caesarean, or assisted by either vacuum or forceps).

3. Results: Table 1 is not clear, and poorly presented. Authors state that several factors were more likely to be associated with low 5-minute Apgar scores. Yet, they do not present any comparison and statistical tests. Please add this important comparison and the relevant P-values to the Table.

The purpose of table 1 is to describe the differences in the prevalence of depressed Apgar score observed in the sample at hand, to assess confounding in the study population, and not to make any inference about differences in a target population. Thus, we are not interested in statistical tests comparing these distributions for possible confounders, but rather the magnitude of the actual observed differences and the degree of confounding that is associated with them (for a more detailed discussion on this methodologic point, please see Rothman KJ, Epidemiology – An Introduction, Oxford University Press, 2002, pp 163-164). With such a large study population, even small differences will be statistically significant, but they will not introduce much confounding. We assessed the confounding more directly by
focusing on the magnitude of the differences. To make our message clear, we have modified the headings in table 1.

4. Results, page 6: What is “protracted gestation?” As an obstetrician I am again not familiar with this term. Please define in the Methods section.

We replaced the imprecise phrase ‘protracted gestation’ with ‘gestation beyond 42 weeks’ on page 7, first line.

5. Discussion: Of major concern is the fact that defiantly not all children diagnosed with epilepsy become hospitalized. While the authors clearly discussed other limitations (such as false positive diagnosis and lack of crucial clinical details), they did not discuss this issue, as is appropriate. Please add another paragraph with this important limitation. Also, they examined only 32 outpatient cases. Can the authors examine more outpatient records?

Clearly, not all epilepsy cases become hospitalized. However, the outcome of interest of our study is epilepsy that does lead to hospitalization. We discuss the outpatient cases to provide additional information for the reader and to give a very rough estimate of their relation to Apgar score, but this was not our focus. We have clarified this point by moving the following paragraph from RESULTS to DISCUSSION and modifying it to read as follows (page 10):

The outcome of interest of this study was a diagnosis of epilepsy that resulted in hospitalization. Not all children diagnosed with epilepsy are hospitalized, and the risk of epilepsy diagnosed among outpatients may exhibit a different relation to five-minute Apgar score. Registration of outpatient visits in North Jutland County started after 1993. Based on a portion of these data, we estimate that about 20 percent of epilepsy diagnoses are made among outpatients, with an incidence of 3/1000 person-years for those with Apgar score below 7 and 0.2/1000 person-years among those with Apgar score of 7 and above. Based on 32 outpatient epilepsy cases observed in these data, we estimated the adjusted risk ratio for outpatient epilepsy to be 9.8 (95% CI 2.6 to 36.6) over six years of follow-up.

6. Discussion: again, please revise “manual turning” to vacuum extraction (?)

In response, we changed the first paragraph in DISCUSSION to include the following sentence (pages 8-9):

We observed greater absolute effect of Apgar score on risk of epilepsy hospitalization among children delivered with the assistance of forceps or a vacuum extractor.

7. Conclusions: I would delete or transfer the “other clinical measurements” since it is not a conclusion of the present article.
In response, we have changed the last paragraph of the manuscript to read as follows:

We found that neither prematurity nor low birth weight was associated with epilepsy hospitalization as strongly as was depressed Apgar score. Apgar score, an easily and routinely collected correlate of a host of perinatal events, may be a useful addition to birth weight and gestational age in predicting epilepsy morbidity among infants.