Title: Risk of Cardio-Respiratory Dysfunction in Preterm Infants Placed in Car Seats: A Cross-Sectional Study

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Author's response to reviews: see over
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To the Editor
BMC

Re Manuscript no 1281212125763714, entitled: Risk of Cardio-Respiratory Dysfunction in Preterm Infants in Car Seat: A Cross-Sectional Study

Dear Editor,

We are in receipt of your letter dated March 26 regarding the revision required to the above-mentioned manuscript and the enclosed comments from the experts in the field who evaluated the manuscript. Please thank the reviewers for their vigorous analysis and very valuable suggestions.

We have considered the points raised and respond as follows:

Response to the Reviewer Dr. Alistair Gunn

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

There is something wrong with the numbers in Table 2. The mean percentages in each of the three binary comparisons (pre-existing conditions, gestational age and pre-discharge weight) should be identical, and also identical to the percentages in the equivalent cell in table 1. e.g. 25 out of the total population of 42 infants had periodic breathing when in the car seat=59.5%. However table 2 shows that 75% of the 16 children<28 week and 61% of the 26 children>=28 weeks

Answer: You were right. There was an error in Table 2. The numbers in the Table 1 and Table 2 were verified and the correction has been made (See Table 1 and Table 2).

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

There are numerous minor errors that need to be corrected. Please note: This is a list of representative suggestions, not a complete listing of redactory errors; detailed, repeated proofread is required.

General:
The authors should refer to cardiorespiratory symptoms. Not dysfunction. The terminology of the stages of testing should be made uniform. In particular as discussed below, the authors should not refer to pre-existing symptoms when they mean symptoms in control. Supine period.
The correction has been made. In the revised manuscript, we used uniform definitions: “Symptoms” vs. “Dysfunction” and “Supine period” vs. “Pre-existing condition” (See manuscript).

Introduction Para 2. this is very difficult to understand. I believe the authors are trying to say something similar to:

Despite this improving knowledge many questions regarding the safe transport of preterm infants remain to be resolved. There is wide inter-hospital variation in the duration of testing in a car seat and the recommendations for infants who fail the test. The risk factors that contribute to the development and severity of cardiorespiratory symptoms in preterm neonates during car seat testing are poorly defined. Only preexisting apnea of prematurity is clearly recognized, 5 and few other risk factors have been systematically studied.

Answer: Thanks for your suggestions. The correction has been made accordingly (See Introduction, Para 2)

Introduction Para 3, final sentence; missing “and “

Answer: The correction has been made. See Introduction, Para 3, sentence:” In addition, the infant was monitored for periodic breathing because of its possible association with oxygen desaturation $^{10, 11}$ as well as cyclical desaturation and reoxygenation of cerebral blood $^{12}$ in the supine position.”

Materials and methods, para 1, 2nd sentence. Power to detect what? The assumptions underlying this calculation must be given.
The number of infants excluded should be given

Answer: The correction has been made. See the following sentences under the Material and Methods: (1) “The inclusion of 42 preterm infants allowed for the determination of a 3-fold increase in the occurrence of cardio-respiratory symptoms during placement in the car seat as compared to the supine position with a statistical power of 0.95 and Alpha $<0.05$ (two-sided)” ; (2) “During the study period three of the discharged infants were not asked to participate in this study because one of the above mentioned condition has been diagnosed during the NICU stay”.

I believe the authors are missing the point about convenience samples. The issue is not power, but the potential for selection bias. The authors should be present evidence that the sample corresponds with their population.

Answer: The correction has been made. See the following sentences under the Material and Methods: “Of 42 sampled infants, 57.1% ($n=24$) were white, 19.1% ($n=8$) were black, 14.3 ($n=6$) were Hispanic, and 9.5% ($n=4$) were of other racial or ethnic groups; 4 (9.5%) were 24 weeks, 12 (28.6%) were 25 to 28 weeks, and 26 (61.9%) were 29-34 weeks gestation. The demographic characteristics of the study groups corresponded with
the neonatal population discharged from the NICU at Saint Peter’s University Hospital.\textsuperscript{13}

*The abbreviation O2 Sat should be spelled out in full in the text.*

**Answer:** The correction has been made (See manuscript).

**Page 4, 2\textsuperscript{nd} para, last sentence, does not make sense. What severity? I believe the authors mean something like:**

Severe cardiorespiratory symptoms were defined as a fall in oxygen saturation to below 80\% and a fall in heart rate to less than 70 beats per minute respectively.

**Answer:** Thanks for this correction; it has been made accordingly with your suggestions. See sentence “Severe cardio-respiratory symptoms were defined as a fall in oxygen saturation to below 80\% \textsuperscript{14} and a fall in heart rate to less than 70 beats per minutes\textsuperscript{15} respectively”, Material and Methods.

**Page 4, data analysis. A comparison cannot be analyzed.**

**Answer:** The correction has been made. See sentence: “Chi-square and one-way ANOVA were used to compare categorical and continuous data, respectively.”

**The threshold P value statement would fit better at the end of this section.**

**Answer:** The correction has been made (see data analysis, Material and Methods).

**The description of the conditional regression analysis is unclear. I think the authors mean something like:**

A conditional regression analysis was performed to evaluate the impact of gestational age, weight at discharge and the presence of cardiorespiratory symptoms in the supine position on the infants risk of cardiorespiratory symptoms during placement in the car seat.

**Answer:** The correction has been made accordingly with your suggestions. See sentence: “A conditional regression analysis was performed to evaluate the impact of gestational age, weight at discharge and the presence of cardio-respiratory symptoms in the supine position on the infant’s risk of cardio-respiratory symptoms during placement in the car seat.”

**Results.**

**First line: delete “the”**
The brackets around “before placement in the car seat” are unneeded.

**Answer:** The correction has been made. See the first sentence under the “Results.”

**Same page, 2\textsuperscript{nd} to last line. Should be and occurred more than 3 times in 11 (26\%) infants.**
Answer: The correction has been made (see sentence: “During the car seat testing oxygen saturation <80% was observed in 13 (31.0%) of the tested infants and occurred more than 3 times in 11 (26.2%) infants”).

Following page (page 6) top, this line is hard to understand. Do the authors mean: There was a significant association between periodic breathing and falls in the O2 saturation to less than 80% (p=0.02, Figure 1).

Answer: The correction has been made, see page 6, sentence: “There was a significant association between periodic breathing and falls in O2 saturation to less than 80% (P=0.02, Figure 1). Thanks for your help.

page 6, first full para, the odds ratio and 95% confidence interval should be given together. Are the authors presenting a univariate analysis followed by the full adjustment in the regression model? This is unclear. If so, both results should be given. ***The authors need to be cautious with the interpretation of the effects of inter related variables. In this case, if the birth weight <2000 is not significant only when included with the other variables, this probably does not actually mean that infants <2000g are not at risk, but rather that their risk is associated with high rate of symptoms even when supine***

Answer: Thanks for your question. In the revised manuscript, the OR and 95% CI were given together and the correction in interpretation has been made. See sentences: “Conditional regression analysis showed that infants with a pre-discharge weight <=2,000 grams were at greater risk for the occurrence of cardio-respiratory symptoms (ORc 4.23, 95%CI 1.02, 25.0). The risk of cardio-respiratory symptoms increased when gestational age and cardio-respiratory symptoms in the supine position were taken into account but did not reach statistical significance (ORA 11.6, 95%CI 0.94, 141.3)”.

Table 1:
Brad-y-cardia
O2: subscript “2” not superscript
Some data cells contain a dash instead of a number. If this represents zero should be used. If there missing data this should be stated in a footer? The missing p values are presumably N.S. or p=0.99

Answer: The correction has been made (see Table 1)

Table 2: The heading “pre-existing conditions” is not ideal. This could be read to mean problems present before this test, whereas the authors actually mean cardio-respiratory symptoms in the supine control period. I suggest that “pre-existing” should be replaced with a “control symptoms” or “symptoms while supine”. All data should be represented at n (%), and dashes should not been used. The precise comparisons made for the significant differences should be stated more clearly.

Answer: All corrections have been made accordingly with your recommendations (see Table 2).
Figure 1 suggests that a fall in O2 saturation to <80% is a more effective discriminator. Should this parameter be used in this table as well?  

Figure 1. 
The authors should consider presenting these data as a table as well. If they prefer to keep this figure, then it must not use the 3\textsuperscript{rd} effect, which is well known to obscure data.

Answer: In according with your suggestion the 3\textsuperscript{rd} effect has been eliminated from Figure 1. We prefer presenting this data in a Figure and in order to be consistent with Table 1 did not change Table 2.

Discussion. 
The discussion is even longer than before, and yet still difficult to follow. The new text is part of the problem. I venture to suggest that the overall readability would be improved by streamlining the author's arguments, and reducing the length by 30%.

Answer: The discussion has been reduced from 921 to 608 words (34%).

Page 7, line one: “ca” should be car
Answer: The sentence that included this error has been eliminated in order to reduce the length of the “Discussion”.

The term “pre-existing” should be used as suggestive above

Answer: The correction has been made.

Concordance should be ‘in accord’ or ‘consistent with’.

Answer: The correction has been made (see sentence: “Our findings are in accord with other investigators ….”).

Page 7, para 2, during car seat testing rather than during the car seat testing

Answer: The correction has been made.

Same para. The associations between periodic breathing and desaturation does not rise the question. The authors presumably just mean something like: Although monitoring for periodic breathing was not included in the AAP recommendations for during pre-discharge car seat testing of preterm infants, our results strongly suggest that it may be of considerable value in identifying infants at high risk of oxygen desaturation during transport.

Answer: Thanks. We used exactly the same sentence that you kindly provided. “Although monitoring for periodic breathing was not included in the AAP
recommendations for pre-discharge car seat testing of preterm infants, our results strongly suggest that it may be of considerable value in identifying infants at high risk for oxygen desaturation during home transport”.

Next para (bottom of page 7). The discussion of the limitations of the study in this and subsequent paras is well meant but it is too and has many distracting redactory errors. The authors should simply list the potential limitations, and the implications of each if any.

Answer: We have corrected this part of the “Discussion” See Discussion Para 3.

The definition of apneas should be in methods, not in the discussion.

Answer: The “definition” has been removed from the discussion.

The statement about standardized classification that follows should be removed.

Answer: That “statement” has been removed.

Subsequent para (first full para, Page 8). This para is much too long. The first half could be removed with no loss of information. If the authors have information that it takes a mean of 2-45 min for their patients to drive home, they should simply say so. The same applies to the references to the duration of monitoring in previous studies.

Answer: The correction has been made in accordance with your suggestions. See “Discussion”.

Para 8, discussion of sleep state. The key statement regarding the risk of leaving infants asleep in a car seat is difficult to understand. Do the authors mean something like:
These observations suggest that if preterm babies are left asleep in a car seat they are likely to be at even greater risk of cardio-respiratory symptoms and consequent episodes of oxygen desaturation. This is of particular concern since there is evidence that a high percentage of episodes of apnea and bradycardia are not detected clinically.27

Answer: Thanks. That sentence has been used in the “Discussion”.

Page 9, 2nd full para. This para, summarizing the conclusions, would be better placed near the beginning of the discussion, where it would help orient the reader and guide subsequent order of discussion.

Answer: You absolutely right. This para has been placed at the beginning of the “Discussion” (see “Discussion”).

The final conclusion is to the point and well written, however, I still wonder if the authors should also note the option of supine transport in a so called car bed
**Answer:** We did point the option of supine transport in a car bed *“There is always the option of supine transport in a car bed.”*

Thanks a lot of your vigorous review and real interest in our research. We would like to have your permission to acknowledge you in our article. If you agree, please send me a note at petroran@umdnj.edu.
Answer to Reviewer Dr. Anne Greenough

General
The authors have answered many of by criticisms. Outstanding, however, are:

1. The authors state correctly this is a convenience sample, but now include that a sample of 42 preterm infants had a statistical power of 0.95 with a alpha<0.05 (two-sided)-but do not give any detail as to what difference this could detect?

Answer: Thanks. By mistake we forgot to include the difference. In the revised manuscript we provide this information: “The inclusion of 42 preterm infants allowed for the determination of a 3-fold increase in the occurrence of cardio-respiratory symptoms during placement in the car seat as compared to the supine position with a statistical power of 0.95 and Alpha <0.05 (two-sided).”.

2. The authors in their response describe what measures were taken to improve the reliability of their measurements but they still do not give the repeatability.

Answer: In this study we use standard equipment and did not test the “repeatability”. The possible difference in the repeated measurements (from the same infant) was not studied. It is however common to any study using standard equipment for continuous monitoring of cardio-respiratory functions for car seat testing in neonates. Perhaps because repeatability is synonymous with “equipment variation” and the variation in the measurements is mostly inherent to the measuring equipment, rather than the personnel. The equipment used (according to manufacturer’s description) has a repeatability of +/- one standard deviation.

In our next study that we plan to investigate the cardio-respiratory function in association with the sleep state in infants during car seat placement ans investigate the repeatability of the cardio-respiratory measurements.

Thanks for your vigorous review.