

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The child's perspective on discomfort during medical research procedures: a descriptive study
AUTHORS	Staphorst, Mira; Benninga, Marc; Bisschoff, Margriet; Bon, Irma; Busschbach, Jan; Diederens, Kay; van Goudoever, Johannes; Haarman, Eric; Hunfeld, Joke; Jaddoe, Vincent; de Jong, Karin; de Jongste, Johan; Kindermann, Angelika; Königs, Marsh; Oosterlaan, Jaap; Passchier, Jan; Pijnenburg, Marielle; Renemna, Liesbeth; de Ridder, Lissy; Tamminga, Hyke; Tiemeier, Henning; Timman, Reinier; van de Vathorst, Suzanne

VERSION 1 - REVIEW

REVIEWER	Jennifer Preston NIHR Alder Hey Clinical Research Facility Liverpool United Kingdom
REVIEW RETURNED	14-Feb-2017

GENERAL COMMENTS	Not sure why there was a comparison with dental procedures? The research team clearly identify the limitations of the study (i.e lack of numbers) but it is a great attempt to tackle the issue of discomfort with research procedures and the recommendations to tackle this discomfort are clearly reported and very much needed.
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REVIEWER	Andrew Davidson Royal Childrens Hospital Melbourne
REVIEW RETURNED	25-Apr-2017

GENERAL COMMENTS	<p>This is an interesting paper that covers an important topic. All too often regulatory bodies make assumptions about what is best or unacceptable for children. These decisions are often based on little evidence. This paper has significant limitations but nevertheless goes some way to address this problem.</p> <p>Could the authors comment on the timing of the evaluation. Would it be better to ask at a later point of closer to the intervention?</p> <p>only healthy children were included but much research is in children that are unwell and or have frequent hospital encounters. the authors acknowledge this limitation but this needs more emphasis as a problem.</p> <p>the authors could report their data in a more informative way. I find table 3 confusing. would a series of box and whisker plots be better.</p>
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	<p>Also I would like it to be clearer what percentage of children had high scores. In some ways this is more informative than the mean as ethics committees worry about the occasional child that has great distress rather than the average child that is a little distressed.</p> <p>I don't think the comparative statistics add much to the paper. It is hardly surprising that children prone to anxiety are more likely to be anxious. The description of the analytical component is a bit sketchy and lacking detail, I would encourage leaving all that out and just report the descriptive stats.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1

1. Not sure why there was a comparison with dental procedures?

Our reaction: in several countries such as the United States, ethics committees have to establish whether the discomfort of paediatric research activities is minimal in relation to children's 'daily life' activities or medical routine examinations that are regarded as minimal discomfort. In line with this interest, we compared discomfort in research to regular dental check-ups because dental check-ups are medical routine examinations – which are considered as low discomfort - that all children in our country encounter approximately twice a year (Note: dental check-ups for children 0-18 years are covered by basic health insurance). In this way, the dental check-ups could function as a 'reference level' of minimal discomfort.

Changes made: we added additional information about the rationale of the comparison with dental procedures.

Page, line number:

- Page 3, lines 45-46
- Page 5, lines 85-86
- Page 7, lines 110-117
- Page 15-16, lines 315-316

2. The research team clearly identify the limitations of the study (i.e lack of numbers) but it is a great attempt to tackle the issue of discomfort with research procedures and the recommendations to tackle this discomfort are clearly reported and very much needed.

Thank you.

Reviewer #2

1. This is an interesting paper that covers an important topic. All too often regulatory bodies make assumptions about what is best or unacceptable for children. These decisions are often based on little evidence. This paper has significant limitations but nevertheless goes some way to address this problem.

Thank you.

2. Could the authors comment on the timing of the evaluation. Would it be better to ask at a later point of closer to the intervention?

Our reaction: we asked the children directly after they underwent the medical procedures because we thought this would correspond to the 'highest' level of discomfort for the children. From other research areas, such as pain research, we know that measuring the impact as close as possible to the event is considered more valid than delayed retrospective measures which bear the risk of recall bias.

Changes made: we added a rationale about the timing of the evaluation of discomfort to the manuscript.

Page, line number: Pages 8-9, lines 155-159

3. Only healthy children were included but much research is in children that are unwell and or have frequent hospital encounters. The authors acknowledge this limitation but this needs more emphasis as a problem.

Our reaction: for this study, we aimed to include both healthy and ill children. However, the majority of the participants in our research appeared to be healthy. Therefore the results might not be representative for ill children. We did an explorative analysis to investigate differences in discomfort between healthy and ill children, which we did not find. Although we cannot draw any conclusions based on this analysis, it might be an indication that being healthy or ill does not influence discomfort.

We do think data on discomfort in healthy children are of great importance because these children (almost) exclusively participate in non-therapeutic studies. These studies have a strict upper limit for the level of discomfort: minimal discomfort, or in some cases a minor increase over minimal discomfort. It is therefore of particular importance to investigate whether the level of discomfort for children undergoing non-therapeutic research procedures - of which a substantial percentage is healthy - is minimal/low. Nevertheless, more research on discomfort in ill children is needed.

Changes made: in the discussion section, we elaborate more on the possible limitations regarding the large group of healthy children in our study.

Page, line number: Page 16, lines 328-331

4. The authors could report their data in a more informative way. I find table 3 confusing. Would a series of box and whisker plots be better. Also I would like it to be clearer what percentage of children had high scores. In some ways this is more informative than the mean as ethics committees worry about the occasional child that has great distress rather than the average child that is a little distressed.

Our reaction: we agree with the reviewer that the data could be provided in a more informative way. We therefore added additional information about the likelihood and magnitude of discomfort, both in the text and in additional graphs.

Changes made:

- We gave a more thorough description of the data in the text.
- We used a series of histograms to provide more insight into the different levels of discomfort the children reported. We used histograms instead of Whisker-Boxplots because it gives a more detailed view of the percentages of the different levels of discomfort, in particular when the median and interquartile ranges of the boxplots are the same. Because of the large amount of information, we decided to provide this information in an appendix (Appendix B. Discomfort – percentages per procedure).
- We decided to keep Table 3 in the manuscript, because readers can see the differences of the

mean scores of the different research procedures at a glance. We added standard deviations to the table and removed the percentages of children who scored 'very' or 'extreme' discomfort.

Page, line number:

- Page 13, lines 249-261
- Appendix B
- Table 3

5. I don't think the comparative statistics add much to the paper. It is hardly surprising that children prone to anxiety are more likely to be anxious. The description of the analytical component is a bit sketchy and lacking detail, I would encourage leaving all that out and just report the descriptive stats.

Our reaction: we agree that it seems self-evident that children prone to anxiety are more likely to be anxious. As this specific relation may be obvious, the relation between anxiety-proneness and the other forms of discomfort may be not. Since anxiety-proneness - and the other demographics we included - are important for ethics committees to consider when they estimate the discomfort of research procedures for the children (e.g. when the level of discomfort for anxious children exceeds a specific level, specific protection is needed) we decided to keep the explorative Spearman correlations between discomfort and the demographics in the manuscript. However, in the revised version of the manuscript we now emphasize that we exploratively studied the association between the demographics and discomfort, rather than to test their predictive value on discomfort (which the use of regression analysis might have suggested).

Changes made: we removed the sections about the regression analysis, and the related sections in the text. In addition, we emphasized our motivation for exploratively studying associations between potential influencing factors and discomfort.

Page, line number:

Added:

- Page 3, lines 46-48
- Page 7, lines 119-122
- Page 14, line 271

Removed:

- Page 11-12, lines 224-226
- Page 14, lines 278-281