Author's response to reviews

Title: Characteristics of highly impaired children with severe chronic pain: A 5-year retrospective study on 2249 pediatric pain patients

Authors:

Boris Zernikow (b.zernikow@kinderklinik-datteln.de)
Julia Wager (j.wager@kinderklinik-datteln.de)
Tanja Hechler (t.hechler@kinderklinik-datteln.de)
Carola Hasan (c.hasan@kinderklinik-datteln.de)
Uta Rohr (u.rohr@kinderklinik-datteln.de)
Michael Dobe (m.dobe@kinderklinik-datteln.de)
Adrian Meyer (adrian_meyer@gmx.de)
Bettina Hübner-Möhler (b.huebner-moehler@kinderklinik-datteln.de)
Christine Wamsler (c.wamsler@kinderklinik-datteln.de)
Markus Blankenburg (m.blankenburg@kinderklinik-datteln.de)

Version: 2 Date: 15 April 2012

Author's response to reviews: see over
Response Letter

*Characteristics of highly impaired children with severe chronic pain: A 5-year retrospective study on 2249 pediatric pain patients*

**Editorial comment:**

Dear Professor Zernikow,

Thank you for submitting your paper to BMC Pediatrics. Your manuscript entitled "Children suffering from severe chronic pain: A 5-year retrospective study on 2249 pediatric pain patients" has been reviewed by specialists in this field (comments below).

The reviewers have now commented on your paper and you will see from the attached comments that they are advising that you revise your manuscript and respond to the major revisions.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point that is being raised when you submit the revised manuscript.

Thank you very much for the opportunity to resubmit our paper. We have carefully addressed the reviewers’ comments and made changes in the manuscript accordingly. Please find our point-by-point response to the reviewers’ comments below.

**Reviewers’ comments:**

Reviewer: Karen Kaczynski

This is a descriptive and correlational study of a large number of children and adolescents treated at a tertiary care facility specializing in the treatment of chronic pain. The study aims to describe key characteristics of these youth as well as to identify factors associated with higher impairment in this population. The goal of this research is to inform how the health care system treats these children and teens. This article has many strengths including large sample size and use of standardized self-report
measures. However, there are significant issues that need to be addressed before this paper can be considered for publication. Comments follow.

Major compulsory revisions:

1. The most significant issue is the lack of importance of this study. Substantial research exists, including epidemiological studies (e.g., King, Chambers, Huguet, et al., Pain, 2011), describing the characteristics and psychosocial correlates of chronic pain in youth, and it is unclear how this paper adds to existing literature. Although the sample size is large, the conclusions drawn are consistent with prior studies, and large sample size is not enough to justify publication. In order to be considered for publication, the authors must make a stronger argument that this paper is important and fills gaps in prior literature.

We agree with the reviewer, that many epidemiological studies exist that have investigated chronic pain in children and adolescents. The most relevant ones conducted between 1991 and 2009 are also included in the meta-analysis by King and colleagues [1].

How this study differs is by having a focus on children with a chronic pain disease associated with significant impairment. Studies prior to this are restricted in the ability to do this because:

1. Previous epidemiological studies on chronic pain focus on children who report the symptom of chronic pain. They may experience permanent or recurrent pain but this may not necessarily require treatment. This is exampled by the study in school children showing many cases resolve spontaneously without treatment [2] and are not necessarily associated with disability, and distress. This raises doubts as to how data from previous studies can be generalized to children with a clinically relevant chronic pain disease as seen in our study.

2. Due to the natural distribution of chronic pain, epidemiological studies include a very small number of highly impaired children. Huguet and Miro [3] for example investigated a school sample of 561 children. Even though 37% of the children were experiencing chronic pain, only 4% (n=22) were actually experiencing moderate pain-related disability and only 1% (n= 6) high pain-
related disability. This would suggest there is insufficient information on this group of children in the literature and hampers generalization of results.

3. Children are often recruited in schools [3-6]. We know from clinical studies that about 20% of the children with a chronic pain disease treated in tertiary care miss more than 50% of their school days [7] making it a real possibility that samples recruited in schools may have a systematic bias, i.e. children highly impaired by chronic pain may be underrepresented in samples as they were not attending school.

The main objectives of this study were to detail the characteristics of children and adolescents with a chronic pain disease in tertiary care and identify factors associated with extremely high impairment within this group. In so doing, this study provides direct information on this previously understudied group and it is anticipated that insights will be gained into the requirements of the health care system to deliver services for this group of children and adolescents.

In accordance with the reviewer’s suggestions, we extended the Background and clarified how this study adds to the current literature (p. 4). In the Discussion section we described more detailed which findings from epidemiological studies could be replicated in our tertiary care sample (pp. 16/17).

2. In general, the conclusion section in the Abstract makes some strong points about why the current study is important (e.g. because chronic pain is associated with poor developmental and functional outcomes). It could better frame the article if the authors made some of these points in the Background section as well, supported with appropriate references.

We expanded the Background section to better frame how this study adds to previous findings (also see comment 1) and why a detailed analysis of highly impaired pediatric chronic patients is important (p. 5).
3. Several variables are included in the study as possible correlates or predictors of impairment. However, these variables are not discussed in the Background. There is a large literature on factors that are associated with impairment related to chronic pain, and this should be included in the introduction. Specifically, the authors should justify why they chose these particular predictors (i.e., age, gender, school impairment) and reference prior research to support their decisions.

According to the reviewer’s suggestions, we have extended our literature review on potential factors associated to impairment. In our study, impairment was not used synonymously with disability. It was defined as an overall construct including pain duration, pain frequency and intensity as well as pain-related school absence and disability (see comment 6 and manuscript pages 5/6). Huguet and Miro [3] used the construct of pain severity, another comprehensive measure of impairment including pain intensity and pain-related disability, and analyzed factors associated with this construct. Pain severity was found to be associated with sex, age, pain location, emotional distress, and health care utilization [3]. We added the results of our extended literature review to the Background (p. 5).

4. Measures should be described in more detail. For each measure, please include a brief description of sample items, response options, scoring procedures, and cut-off scores, if appropriate. Also provide reliability and validity information and internal consistency statistics for the current population.

We added more detailed information on the measures used in this study in the Methods section (pp. 8-10).

5. Completing missing items on child questionnaires with parent proxy report is not acceptable. Research has shown that child- and parent-report are inconsistent, particularly regarding internalizing and somatic symptoms (e.g., Kröner-Herwig, Morris, Heinrich, et al., Clin J Pain, 2009). Given the large N, a proportion of missing data should not be too problematic.
In this study, data for pain characteristics (pain location, pain frequency, pain intensity) was replaced by parent proxy report in case of missing values. Other information, such as depression or anxiety scores, was not replaced by parental reports.

We changed the sentence on page 10 to make this point more clear.

Since data for this study was gathered retrospectively from the clinical letters, where missing values from children are automatically replaced by parent reports, we cannot deliver data without replacement of these missing values. We examined the data of 529 children, who presented in the pain clinic between July 2009 and June 2010 (Wager et al., in prep.). In this subsample only 2% of missing child data on pain intensity was replaced by parent information.

We added this limitation to the Discussion section (p. 19).

6. Please explain how the criteria were selected for assignment into the high impairment group. Were these cutoffs used in any other studies, or is there evidence that they are meaningful in predicting outcomes (e.g. future impairment without treatment)?

Criteria were used in clinical practice for assignment to inpatient or outpatient treatment and were applied in previous studies [8,9]. We added this information on page 10.

7. While dichotomizing variables can facilitate clinical interpretation, it can also result in a loss of information. Where dichotomies were created, it would be helpful to know on what basis this was done (mean split, clinical significance?) and a justification for this decision.

We are very aware that dichotomizing continuous variables comes along with a loss of information. Since this study aims at the explicit presentation of factors associated with extremely high impairment, we consciously decided to take the loss of information in favor of clinical interpretability. Dichotomizing was created with regard to content. Age, for example, was divided into children and adolescents (also compare
comment 9); anxiety and depression scores were divided into normal and increased values (T-value>60).

We added the information of dichotomizing on page 11.

8. Several variables reported in the results have not been described in the Background or Measures (e.g., fear of exam, school aversion). These variables should be described and the method of assessing them more clearly defined.

We added this information accordingly in the Methods (pp. 8-10).

9. How were the age cutoffs selected? Because there are so many groups used and comparisons made, interpretation of some results becomes unclear. For example, how is the reader to interpret the finding that distribution of pain location did not differ between genders except in 11 to 14-year-olds? A developmental justification is needed to support the decision to separate the sample into so many distinct age groups rather than looking at age as a continuous variable.

Children were assigned to age groups for a better readability and interpretation of results. Additionally, dividing children into groups instead of using the age as a continuous variable allowed detecting non-linear relations between age and other variables. Differences in pain characteristics were expected within the different ages of the pediatric sample [4,10]. Therefore, children were classified into groups depending on their developmental stage and social role. We divided children into five age groups. Children aged up to three years are infants and toddlers (0-3y); from the age of four to six the German child attends kindergarten (4-6y); this time is considered as early childhood. After this phase the child enters primary school, middle childhood (7-10y), and then transfers to secondary school. Adolescents (age 11y and older) were divided into two groups (11-14y; ≥15y). The justification was added to the manuscript text on page 8.
10. This paper has 6 tables and 4 figures, which seems excessive. The authors should attempt to consolidate the tables or report some of the data in summary format in the text.

We combined tables 3, 4, and 5 (Characteristics of pain, Pain-related disability and school absence and emotional distress) and reduced the number of categories for pain frequency, school absence and number of previous physician. Information on clinically relevant anxiety and depression scores were deleted from the table as it was already reported in the text. This shortened the information in the tables and cut down the number of tables to 4.

11. Paragraph 4 reports the preponderance of girls in the sample and describes adolescent girls as “a very vulnerable group.” The next paragraph reports that sex differences are minimal and that age differences are most meaningful. These two conclusions seem contradictory and efforts should be made to integrate these findings.

The statement that girls are a very vulnerable group refers to the elevated number of girls in this sample of tertiary care chronic pain patients (see figure 1) and findings from previous epidemiological and clinical studies which report a higher number of females with chronic pain than males (see manuscript page 16). Next to an increased rate of chronic pain in girls, epidemiological studies also found sex differences, such as increased pain intensity and higher rates of headache and abdominal pain in girls [5,10]. These sex differences could not be replicated in our sample. Therefore, we mention that sex differences are minimal. Importantly, this statement refers to boys and girls in our tertiary care sample.

We understand that our remarks were rather misleading and changed the wording to make this clear (pp.16/17).

12. Would another possible reason that adolescents seen at this tertiary care facility have had longer illness durations and previous treatment failures be that the healthcare system is actually functioning well, in attempting to address these issues in primary and secondary care settings before sending a smaller portion who fail at these levels to
tertiary care? Some more clarification of the reasoning behind the strong conclusions of the last paragraph appears warranted. Additionally, alternative explanations should be included.

In case children did not experience a sudden deterioration of their pain condition, we do not consider the pain durations reported in our sample a result of a well-functioning health care system. We elaborate this further on page 17.

We agree with the reviewer that alternative explanations may be possible. Since we did not control for pain severity in the past, these findings could also be explained by developmental changes in the pain condition during adolescence. Adolescence is a vulnerable period of life. It may aggravate a preexisting pain problem and other problems associated with it (e.g. problems in school, emotional distress) and thereby turn it into a condition that requires treatment. We added this alternative explanation to the Discussion section (p. 17).

Minor essential revisions:

13. It would be helpful for authors to clarify the meaning of “severely impaired” in the abstract. Is this in terms of the patients’ functioning?

We have defined impairment further.

14. Please clarify the prevalence rates in the first paragraph of the Background. Is this lifetime prevalence? Of what severity of chronic pain/what level of functional impairment?

The studies reported all assessed the 3-months-prevalence. We added this information to the Background (p. 4).

The question concerning the level of pain severity is an important issue in our manuscript. Pain severity and pain-related impairment are not taken into consideration in most epidemiological studies reporting chronic pain. One exception is the study by Huguet and Miro [3] (see comment 1).
15. In the second paragraph of the Background, are these statements about existing research in adults or in youth?

These are pediatric studies. We added this information (p. 5).

16. The treatment model in the clinic as described in the Methods implies that organic causes for the pain have been ruled out (e.g., they “prevent further unnecessary diagnostic or medical intervention”). This needs to be explicitly stated.

Our approach to pain is through the bio-psycho-social model and while the child is assessed for potential organic causes we do not exclude children with organic causes from the clinic. Importantly, the organic condition alone does not explain the severity of the pain, since other dimensions modulate the pain experience.

Our goal is to prevent unnecessary diagnostic interventions, which may have already occurred or were not indicated by the patient’s assessment. To make this more explicit, we changed the wording (p. 7)

17. The Total row of Table 1 should be more prominent, as general demographic data are of interest, not just demographic data broken down by pain location.

We put more emphasis on this data by plotting it bold.

18. Figure 1 needs a label on the Y axis.

We changed this accordingly.

19. It seems as though Figure 2 could be improved by presenting the data in another format. As it is, the figure emphasizes the association between age at first appointment and age of pain onset, which is not a surprising finding. What is an interesting finding is
the relationship between years since pain onset and age at first appointment. Could the figure be altered to emphasize that finding?

We created an alternative presentation of results to highlight the information suggested by the reviewer. The table and figure underneath present those results.

Table: Age at first presentation (in years)

<table>
<thead>
<tr>
<th>time since pain onset (in years)</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 years</td>
<td>734</td>
<td>11.42</td>
<td>3.395</td>
<td>12.00</td>
</tr>
<tr>
<td>1-2 years</td>
<td>465</td>
<td>10.91</td>
<td>3.777</td>
<td>11.00</td>
</tr>
<tr>
<td>2-3 years</td>
<td>270</td>
<td>11.43</td>
<td>3.431</td>
<td>12.00</td>
</tr>
<tr>
<td>3-4 years</td>
<td>193</td>
<td>11.30</td>
<td>3.250</td>
<td>11.00</td>
</tr>
<tr>
<td>4-5 years</td>
<td>149</td>
<td>11.64</td>
<td>2.989</td>
<td>11.00</td>
</tr>
<tr>
<td>5-6 years</td>
<td>114</td>
<td>12.13</td>
<td>2.799</td>
<td>11.50</td>
</tr>
<tr>
<td>6-7 years</td>
<td>70</td>
<td>12.06</td>
<td>3.040</td>
<td>12.00</td>
</tr>
<tr>
<td>7-8 years</td>
<td>63</td>
<td>12.71</td>
<td>2.345</td>
<td>13.00</td>
</tr>
<tr>
<td>8-9 years</td>
<td>42</td>
<td>12.62</td>
<td>2.273</td>
<td>12.50</td>
</tr>
<tr>
<td>9-10 years</td>
<td>34</td>
<td>13.56</td>
<td>2.452</td>
<td>14.00</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>56</td>
<td>15.05</td>
<td>1.872</td>
<td>15.50</td>
</tr>
<tr>
<td>total</td>
<td>2190</td>
<td>11.56</td>
<td>3.399</td>
<td>12.00</td>
</tr>
</tbody>
</table>
Even though the general idea, that an increasing time since pain onset is associated with older age at the first appointment, becomes apparent, we do not think that the information in this figure transports the relevant results in a more descriptive way. Since reviewer 2 considered Figure 3 highly informative, we would like to keep the figure as it was in our first submission (with slight changes suggested by reviewer 2), if reviewer 1 agrees.

20. **Figure 3 seems to be presenting a lot of information at once, and could be improved by labeling bars for depression and anxiety in the footnote to the table and/or choosing between presenting means or percentages above cutoff rather than including both.**

   We tried to make this figure easier to read by dividing the two different measures.

21. **In the first paragraph of the Discussion, the authors describe impairment in “normal leisure time activities.” How was this assessed? A measure of leisure activities was not described in the methods.**

   We refer to the PPDI value (Paediatric Pain Disability Index [11]), which measures the impairment in every day activity. We changed wording accordingly (p. 15).

22. **The first sentence in the third paragraph of the discussion is a run-on sentence and the point of this sentence is not clear.**

   We changed the whole paragraph.

23. **The authors draw conclusions regarding the prevalence of comorbid psychiatric conditions based on elevated scores on anxiety and depression questionnaires. It is not possible to make a diagnosis based on a questionnaire. Rather than discussing comorbid diagnoses, the authors should discuss the prevalence of elevated symptoms of anxiety and depression.**
We changed this accordingly on page 16.

24. The authors cite data on the lack of appropriate treatment facilities for youth with chronic pain in the conclusions. Given that this was one of the goals of this paper, this information should be presented earlier, in the Background.

We included this point in the Background (p. 5), moved the part in the discussions section forward and adapted it (p. 18).

Reviewer: Leora Kuttner

Reviewer's report:

This descriptive study deserves publication. The data set of over 2,000 children is remarkable in the field of pediatric chronic pain.

Major Compulsory Revisions:

NONE

Minor Essential Revisions:

Under Statistics 3rd Parag: “All variables are dichotomized” It is unclear how this was achieved. I’d recommend providing an example e.g. pain location.

We added this information (please see Reviewer 1/comment 7 and manuscript p. 11)

Figure 2 is a highly informative graph. I’d recommend dropping ages 18 and above as the Ns are so small that it detracts from the generality of the trend line

We combined ages 18 and above. The result still deviated from the trend line, but the N is bigger.
In Figure 3 the height of the bars appears to be inconsistent with the scale on the right hand side of the figure e.g. bar of 23.7% seems too high

We corrected the incorrect value in this figure.

Figure 3 also merits more discussion beyond the one line on Pg 10, particularly with regard to groups showing significant differences.

We described the results being presented in Figure 3 more detailed in the Results section (p. 14) and in the footnote of the figure.

Discretionary Revisions:

Under Procedure : Parag 1. ‘T value’ It would be helpful as a reminder to the reader that these are standard scores with a mean of 50 and SD of 10.

We added this information on page 9.


