Author's response to reviews

Title: Regional perinatal mortality differences in the Netherlands; care is the question?

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Version: 3 Date: 17 February 2009

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

We appreciate the opportunity to resubmit our manuscript ‘Regional perinatal mortality differences in the Netherlands; care is the question?’ to BMC Public Health.

We would like to thank the reviewers for their valuable comments on our work. Based on these comments we have adjusted our manuscript. Below we provide a detailed description of the changes that were made in relation to the comments from the referees.

We hope that our manuscript is now suitable for publication in BMC Public Health.

Yours sincerely,

On behalf of all authors

Miranda Tromp

Amsterdam

February 17th, 2009
Title: Regional perinatal mortality differences in in the Netherlands; most prominent from 32+0 weeks gestational age onwards.

Version: 2 Date: 23 January 2009
Reviewer: Bengt Källén

Reviewer's report:
I think the authors have made a good job of the revision. Here are a number of minor details which I asked about which have not been answered in the manuscript.

1. The actual model in the logistic modelling. The fact that maternal age has a U-shaped relationship must be taken into consideration when maternal age is entered as an explanatory variable in a model and it is not clear from the text how and if this has been done. The same problem with parity and then there should be an interaction term between age and parity, I think. The authors have hopefully thought about this but it is not clear how it was solved.

We agree with the reviewer that the U-shaped relation of maternal age and parity should be addressed. We have taken the U-shaped relation of maternal age and parity with perinatal mortality into account by using categorical variables. Maternal age and parity were entered as categorical variables in the model with the category with the lowest mortality as reference. For maternal age the category 20-34 years is the reference category and the category <20 and ≥35 have a higher risk on perinatal mortality compared to the reference category – satisfying the U-shaped relation. One might argue that using only 3 categories for maternal age not fully justifies the U-shaped relation, we have also conducted the analyses with 5 categories (see table below). The regional effect remained the same and we prefer the model with fewer categories. Parity was handled in the same way, where parity 1 is the reference category and nulliparous women and women with parity 2 or higher have a higher risk than the reference category.

We tested for interaction between maternal age and parity, however the interaction term was not significant (p-value=0.15). The region effect remained the same after inclusion of the interaction term. In addition, we repeated the analysis for nulliparous and multiparous women separately and the same regional effect was found in both groups with an increased risk in the northern region.

Table Perinatal mortality (22⁺0 weeks – 6 days) risk per region after adjustment for risk factors (with maternal age in 5 categories instead of 3).

<table>
<thead>
<tr>
<th>Adjusted model</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>1.11</td>
<td>1.03-1.20</td>
</tr>
<tr>
<td>East</td>
<td>1.04</td>
<td>0.98-1.10</td>
</tr>
<tr>
<td>West</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>South</td>
<td>0.97</td>
<td>0.92-1.03</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20 years</td>
<td>1.40</td>
<td>1.24-1.59</td>
</tr>
<tr>
<td>20-24</td>
<td>1.14</td>
<td>1.07-1.22</td>
</tr>
<tr>
<td>25-34 years</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>35-39</td>
<td>1.26</td>
<td>1.19-1.33</td>
</tr>
<tr>
<td>≥ 40 years</td>
<td>1.67</td>
<td>1.49-1.87</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity 0</td>
<td>1.40</td>
<td>1.33-1.47</td>
</tr>
<tr>
<td>Parity 1</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Parity 2+</td>
<td>1.31</td>
<td>1.24-1.40</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Non-Western</td>
<td>1.34</td>
<td>1.27-1.42</td>
</tr>
<tr>
<td>Urbanization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. The question on congenital anomalies has to some extent been clarified. It would have been nice to see exactly what conditions that were removed and how frequent these were which would give an indication on how complete ascertainment has been. I don’t think this is very important, however, and it can probably be left as it is.

We have no information on the completeness of ascertainment of congenital anomalies in the registry. The presented figures might be an underestimation of the true prevalence. However, the overall prevalence of severe congenital anomalies is about the same for all regions (Table 5), which indicates that there are no regional differences in the ascertainment. The elevated mortality among children with severe congenital anomalies in the northern region is remarkable.

3. The only thing which I think the authors must re-consider is the title of the paper. I suggested that the title should somehow include a message that one not only describes differences but also try to identify causes. What the authors have done now is to add another message, that the major differences were among infants born after week 31 which I do not think is that important that it has to be put in the title.

We changed the title to: ‘Regional perinatal mortality differences in the Netherlands; care is the question?’

Reviewer’s report
Title: Regional perinatal mortality differences in in the Netherlands; most prominent from 32+0 weeks gestational age onwards.
Version: 2 Date: 15 January 2009
Reviewer: Inez M.A. Joung
Reviewer’s report:
The authors have adequately addressed the comments and questions I posed previously. I have no additional comments and advise acceptance of the manuscript.
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer’s report
Title: Regional perinatal mortality differences in in the Netherlands; most prominent from 32+0 weeks gestational age onwards.
Version: 2 Date: 29 January 2009
Reviewer: Shingairai Feresu
Reviewer’s report:

Review
The paper is greatly improved, however I still have some concerns.

1. I am not sure about this new title either try another one, I think.

   We changed the title to: ‘Regional perinatal mortality differences in the Netherlands; care is the question?’

2. There needs to be consistency in how the ‘regions’ are identified in this paper, is it Northern region? region north? Most readers would identify with the former

   We now consistently use ‘Northern region’ throughout the text.

3. Please put main cities in the map in Figure 1. We need to clearly know which region Amsterdam lies, and even in the methods where you describe the regions on page 6.

   We replaced Figure 1 with a map including the four largest cities in the Netherlands (Amsterdam, Rotterdam, Utrecht and Den Haag), all main cities lie in the Western region.

4. At the beginning were you report results from the region put in parenthesis for example Northern region (which is most rural) and Western region (which is most urban) that way the reader gets used to what the regions mean, do it once then I think it will sink thereafter.

   Thank you for this suggestion to make the difference between the regions more clear, we added this text in the result section.

5. On page 5 definitions of SB, perinatal mortality SB rate, why is perinatal mortality not per 1,000 live births, if you can justify your thinking?

   The WHO definition for perinatal mortality is to include stillbirths (from $22\,^{\circ}0$ weeks gestation onwards) and early neonatal deaths (0-6 days) and calculate the rate per 1,000 total births (live births and stillbirths).

6. On page 8, I am a little confused when you describe the five groups of preterm birth in methods last paragraph, what do you mean by without severe congenital anomalies, what do you mean by severe, and how many were in that category? do you just want to exclude all congenital anomalies? clarify further what you mean

   The clinical risk groups were based on the mediating risk factors gestational age and severe congenital anomalies. The severe congenital anomalies formed a separate group in the clinical risk group analysis with a different perinatal mortality rate. Therefore the other groups are without severe congenital anomalies. Severe congenital anomalies were defined as anomalies which are either highly fatal or as anomalies potentially detectable by ultrasound and severe enough for optional late termination of pregnancy (for example: anencephalus, encephalocele, spina bifida, hydrocephalus, hypoplastic left heart, bilateral renal agenesis, Down syndrome and trisomie 13 or 18).

7. On page 9 first sentence, give us the overall Northern region perinatal, and say with highest rate in ... provinces......

   We changed the sentence accordingly.

8. Last paragraph first sentence, need to say "significantly higher compared to Western region". Last sentence what does “full adjustment” mean- clarify

   We changed the wording of the first sentence, last paragraph as suggested. Full adjustment means adjusted for all considered risk factors: maternal age, parity, ethnicity, social economic status and degree of urbanization. We adjusted the text to clarify.

9. Discussion page 11 were you say Dutch perinatal mortality, do you mean The perinatal mortality in the Netherlands, since some of the population may not be Dutch by ethnicity, that sentence has to be corrected
We meant the perinatal mortality in the Netherlands and changed the wording accordingly.

10. The discussion needs to be tightened. The points are not connected to make a meaningful story, it's like things are hanging. Examples on page 12 Treffers et al., Mackenbach et al. how do they relate to your findings, that whole paragraph and the next need to be clarified, to flow and to connect. The northern region has bad outcomes why is that, what do you postulate, what did other studies find? What do you propose to be done to resolve or at least address this situation. It can be written very clearly.

We found a higher risk for perinatal mortality in the northern region and we tried to understand the influence of risk factors and mediating risk factors. We corrected for factors found by others to relate to perinatal mortality (social economic status and urbanization degree) which we mention in this paragraph in the discussion. In our study, adjustment for these factors only explained a small part of the found differences. Therefore, in the next paragraph we more generally report on possible causes of regional differences and which remain as possible causes after the adjustments described in the study. We now removed the last sentence from the former paragraph and added it to the next paragraph for a better connection between the paragraphs. We also rephrased the paragraph where we relate our findings to findings by others. We end the paragraph with recommendations for future research into the role of health care factors, detailed analyses on clinical risk groups and audit studies on perinatal mortality cases.

11. I think the abstract will need the same adjustment, once the discussion is tightened.

The registry data do not allow us to draw firm conclusions on the reason for the increased perinatal mortality in the northern region. We can only conclude that the differences remain after adjustment for known risk factors available in the registry and that indications exist for a possible role of health care factors based on the risk group analyses.

12. You suddenly talk about 40 regions on page 12, I thought they were 4, or is it a typo?

The 40 regions were used in a previous study on regional differences in the Netherlands that we report on in the discussion. The text has been changed to make clearer that we talk about another study here.

13. On page 13 towards the end suddenly you talk about congenital anomalies in north region, do we know the distribution of these, and what about severe/ all - need to clarify.

In table 5 the prevalence and mortality risk of severe congenital anomalies is presented per region. From this table it can be seen that the mortality risk for children with severe congenital anomalies is higher in the northern region, which is mentioned in the last part of the result section. In the discussion section we relate to this point.

14. Table 3 should have in footnote what each model was adjusted for as done in the response table in letter

We added a footnote to table 3 with the information on adjustment in model I and II.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: 'I declare that I have no competing interests'