Author's response to reviews

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

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Version: 2 Date: 30 December 2008

Author's response to reviews: see over
To the editor

Dear editor,

We appreciate the opportunity to resubmit our manuscript ‘Regional perinatal mortality differences in the Netherlands; most prominent from 32\textsuperscript{+}0 weeks gestational age onwards’ 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
December 30\textsuperscript{th}, 2008
Reviewer's report 1
Title: Distinct regional differences in perinatal mortality in the Netherlands
Version: 1 Date: 11 November 2008
Reviewer: Bengt Källén

Reviewer's report:
This is a well written and interesting paper. The authors pose a clear question and use a national perinatal register as source of information.

Major compulsory revisions
1 Title of article. The title just tells that there are regional differences in perinatal mortality but the article also tries to explain these differences. ‘Should this not be apparent in the title?’

We changed the title to ‘Regional perinatal mortality differences in the Netherlands; most prominent from 32^{0} weeks gestational age onwards’.

a) On p 5 it is said that the register used contains information on about 96% of all deliveries in the Netherlands. The drop-out rate is not large but may be skewed. At least in our country, we know that the cases missed in the central medical birth register are to some extent selected and with an excess of complicated deliveries, including infant deaths, multiple birth and severe congenital malformations. This may not be so in the Netherlands but I think this must be discussed. Furthermore, it is not clear if the drop out rate is the same in the different regions. As the authors know that there is about 4% missing, I suppose there is an administrative register which can be used for checking the completeness of the data in the various regions.

A pilot study was conducted to link the perinatal registry data with civil registries which showed that more fetal deaths were registered in the perinatal registry than in civil registries especially the very premature fetal deaths (KIK technical report 2007-07, http://kik.amc.uva.nl). Regional figures from civil registries are only available on live born children and with no specification of singleton and multiple births. When we compared the regional data from the perinatal registry to civil registries over the period 2000-2004, the region south had the highest completeness and completeness was comparable for the three other regions. The 4% missing is based both on comparison to civil registries and on knowledge of non-participating centers in a specific year. The perinatal registry and the civil registration have different inclusion criteria and are therefore not totally comparable.

b) On p 5-6 it is said that the preterm birth and low birth weight were analyzed as mediating outcome measures. The authors have chosen <37 weeks, <2500g and low Apgar (<7 at 5 minutes). These are cut-off values which are often used in reproduction epidemiology but if one is interested in risk factors for perinatal death, I think one should choose lower limits, perhaps <32 week, <1500g weight (or even <1000g), and <4 Apgar score. Later on they distinguish between preterm and very preterm but this should be clarified already in the methodological description.

We changed the cut-off values for the mediating outcome measures for perinatal death in table 1. We agree with the reviewer that lower limits are more appropriate in relation to perinatal death. With the lower cut off values the region North has significantly higher prevalence of preterm birth <32.0 weeks and low birth weight <1500 gram. No differences were observed in low ApgAR score <4.

The clinical risk groups are classified based on gestational age and severe congenital anomalies. The groups are described in the methods section and a table is added to the paper (table 5) with the prevalence and mortality risk by region for the distinct groups.

c) On p. 8 the authors describe the statistical analysis as logistic modeling, but no further details on the actual modeling is given. They have, for instance, used maternal age as one dependent variable. Was that a linear regression or did one take into consideration the U-formed association between maternal age and perinatal death risk (seen in Table 3). If you
have a U-formed association and puts a straight line into the model, the association may seem non-existent. The same is true for parity and to this can be added that maternal age and parity interact: low maternal age and high parity and high maternal age and low parity are high risk strata. It is not clear how these problems have been solved. By giving each maternal age stratum a 0-1 variable etc.??

The reviewer is correct in that it was not described in the method section how we modeled the maternal age and parity. We used categorical variables in the model with the category with the lowest mortality risk as reference. This information is added to the method section and the adjusted results are also shown in table 3.

d) Also on p. 8 the categorization into severe congenital anomalies and without such anomalies is described but no definition of what is meant with severe congenital anomalies. There are many severe anomalies which are no death risks (e.g., absent of a hand). I suppose what would have been more relevant was the presence of a malformation which carries a marked death risk, e.g., diaphragmatic hernia and omphalocele but not gastroschisis. Anyway, the authors must describe how they defined severe congenital anomalies and tell how they were identified and give some ideas about prevalence at birth, total and by region. – The authors do not mention the phenomenon on prenatal diagnosis and selective abortion. Could regional differences in the extent and efficiency of prenatal diagnosis (and perhaps acceptance of induced abortion when a severe malformation is found) contribute to the variability in death rate (p. 13).

We selected congenital anomalies as ‘severe’ based on their mortality risk. 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). This information is added to the method section. We incorporated a new table with the prevalence and mortality risk of the five clinical risk groups for each region where the prevalence of severe congenital anomalies by region is depicted (table 5). The prevalence of severe congenital anomalies is about the same for all regions. No data is available on variation in prenatal diagnosis and acceptance of induced abortion when a severe malformation is found. However, we considered severe congenital anomalies from 26+6 weeks gestation onwards and induced abortion after prenatal diagnosis will be in an earlier stage of pregnancy.

e) The authors miss important data on smoking and BMI on an individual level. They do adjust for regional differences between these characteristics which I suppose is as close they could come. I suppose these data refer to the smoking rate in the population and not to smoking among pregnant women (which may differ) and the same is probably true for BMI. The authors should specify what type of data they have. They quote papers from other parts of the world where it is made likely that socioeconomic and ethnic adjustments take care also of smoking and BMI. If this is true in the Netherlands is just a guess, I suppose. How do the authors define heavy smoking (Table 2)? The rates given in that Table are very low which indicates that they have a rather high cut-off rate. Also moderate maternal smoking is a risk factor for perinatal mortality ref. 23).

The data on smoking and BMI on a province level refer to data on women within the reproductive age, but not specifically to pregnant women as this data is not available. One of the papers that we quote is indeed from the Netherlands. The only item registered in the Dutch perinatal registries is heavy smoking and the very low prevalence shows that this is an underestimation of the true prevalence of smoking during pregnancy. This is why we displayed the prevalence by region in table 2 and decided not to include this in the model shown in table 3. If we included severe smoking in the adjusted model from table 3, the results did not change.

3. Data presentation.
a) Figure 1: I must confess that I do not understand this Figure. What do the black circles mean? Obviously they should mark the province contribution to the total birth rate. The
proportions of births are given as percentages in Table 1 and I think that is enough. Figure 1 could be kept in order to describe the geography if that really is of importance for the reader but I think the black circles are only confusing.

We replaced figure 1 by a new figure of the Netherlands for describing the geography and left out the black circles.

b) Figure 2. What does this Figure add? Rates of stillbirths per region and province – but those numbers could equally well be given in a Table which could contain the actual numbers (similar to Table 1). I would suggest that Table 1 contains data on total number of children, number of preterm birth (preferably for <32 weeks), low birth weight (preferably for <1500 or <1000g) and low Apgar score (preferably <4) and that all information on stillbirth, early neonatal death and perinatal death is given in a separate table.

We included the stillbirth and neonatal death rates in table 1 and removed figure 2. We adjusted the cut off values of the severe outcomes as suggested to preterm birth <32 weeks, low birth weight <1500 gram and low APGAR score to <4.

Minor revisions
The authors use weeks.days for gestational length which is confusing because it looks like a decimal point. Usually one writes weeks+days, e.g., 20+0-25+6.

We changed the format of gestational age as suggested.

P 6 2 lines from bottom: I think data is plural and that it should be these data...

Changes were made.

Level of interest: An article whose findings are important to those with closely related research interests

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.

Reviewer’s report 2
Title: Distinct regional differences in perinatal mortality in the Netherlands
Version: 1 Date: 12 November 2008
Reviewer: Shingai Feresu
Reviewer’s report:

Major Compulsory Revisions
Re: “Distinct regional differences in perinatal mortality in the Netherlands”

Review
This paper explores the regional differences in perinatal mortality an important indicator of maternal care in the Netherlands and as such is an important local paper. In trying to read it, it is very difficult to understand the regions each time they are mentioned without reverting to the map or going back to methods to figure out what the authors are presenting. The paper may be important and appropriate for national and local audience.

I have some suggestions for on the paper to improve its appeal to the international readership:
1. Amsterdam, may have to stand out by itself as this city may be so different from the rest of Holland, both in composition, health behavior and treatment opportunities.
The reviewer is correct in that Amsterdam is different from the rest of the Netherlands as a large city. However, when we removed Amsterdam from the region West, the results on region did not change (see table below). Another study will focus on large city risks, which is not the focus here. We now included the adjusted value of urbanization in table 3.

Table Perinatal mortality (22^{10} \text{ weeks} – 6 \text{ days}) risk per region after adjustment for risk factors, excluding Amsterdam.

<table>
<thead>
<tr>
<th>Adjusted model excluding Amsterdam</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region</strong></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>0.97-1.10</td>
</tr>
<tr>
<td>West*</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>South</td>
<td>0.97</td>
<td>0.91-1.03</td>
</tr>
<tr>
<td><strong>Maternal age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20 years</td>
<td>1.35</td>
<td>1.18-1.54</td>
</tr>
<tr>
<td>20-34 years</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>≥ 35 years</td>
<td>1.32</td>
<td>1.25-1.40</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity 0</td>
<td>1.43</td>
<td>1.36-1.50</td>
</tr>
<tr>
<td>Parity 1</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Parity 2+</td>
<td>1.29</td>
<td>1.21-1.37</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Non-Western</td>
<td>1.33</td>
<td>1.25-1.41</td>
</tr>
<tr>
<td><strong>Urbanization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very urban</td>
<td>0.93</td>
<td>0.87-1.00</td>
</tr>
<tr>
<td>Middle</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Very rural</td>
<td>1.03</td>
<td>0.97-1.09</td>
</tr>
<tr>
<td><strong>SES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.14</td>
<td>1.07-1.20</td>
</tr>
<tr>
<td>Middle</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>High</td>
<td>0.90</td>
<td>0.85-0.95</td>
</tr>
</tbody>
</table>

Adjusted for maternal age, parity, ethnicity, urbanization and SES.

2. The more pressing issue is maybe to present this paper as rural versus urban, which although different for different parts of the world is universally at least understandable.

We were interested in the regional variation in perinatal mortality in the Netherlands. The level of urbanization was included in the model in three categories: very urban, middle and very rural. The regional effect is more than just the urbanization effect as the effect remains visible after adjustment for urbanization. However, the adjusted odds ratios for the other factors in the model besides region were not visible in table 3. We now show that living in an urban area is a risk factor when analyzed crude, but becomes a protective factor for perinatal mortality in the adjusted model. When the regional effect is left out of the model, the urbanization effect is only a little bit stronger (OR for very urban 0.91, 95% CI 0.86-0.96).

3. The authors need to explain why they chose 22 weeks of gestation as cut off. There are several definitions of cut off based on WHO - 20 weeks, viability – 24 weeks or 28 weeks depending on where one resides.
The WHO definition for perinatal mortality is to include pregnancies from 22 weeks of gestation onwards and exclude pregnancies with a birth weight below 500 gram in case of unknown gestational age (reference: WHO Neonatal and Perinatal mortality – Country, Regional and Global Estimates, WHO 2006). We used these definitions to determine our study population.

4. Table 3 has crudes for all the variables, but adjusted for just region – uniformity in presenting results may help enrich the paper.

We included the adjusted odds ratios for all variables in the adjusted models in table 3.

Level of interest: An article whose findings are important to those with closely related research interests

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'

Reviewer’s report 3
Title: Distinct regional differences in perinatal mortality in the Netherlands
Version: 1 Date: 24 November 2008
Reviewer: Inez M.A. Joung

Reviewer’s report:

An interesting study, which might certainly add to our knowledge on this topic, when the major compulsory revisions can be adressed satisfactorily

Major Compulsory Revisions

- the authors differentiate between ethnic groups by dichotomizing between Western (native Dutch and other Westerners) and non-Western (including different ethnic groups like African/Surinamese Creole, Surinamese Hindustani, Moroccan and Turkish). However, in a previous Dutch study on ethnic differences in infant mortality (Troe EJ, et al. Paediatr Perinat Epidemiol 2006;20:140-7) it was shown that the mortality risk in the early neonatal period (defined as death in the first week of life) was elevated for the Surinamese and Antillean group, but not for the Turkish and Moroccan group. In the Turkish group, the largest ethnic minority group in the Netherlands, the point estimate for the mortality risk in the early neonatal period, was even smaller than for the native Dutch population (although not statistically significant). By pooling the data of the large ethnic minority groups in the Netherland, the ethnic differences in perinatal mortality might well be leveled out, which might have biased the outcomes of the study, especially given the fact the division of ethnic minority groups in the Netherlands is quite skewed with the largest proportion living in the western region. What are the outcomes in case when adjustment is made for the separate ethnic minority groups?

The reviewer is correct in that the level of perinatal mortality differs by ethnic group. The perinatal mortality is elevated in all ethnic groups when compared to the native Dutch, with the exception of other Westerners. This is why we adjusted for the non-Western group as a whole. We repeated the analysis with adjustment for the separate ethnic minority groups which did not change the regional effect. In the region North the number of non-western women is the lowest.

The elevated perinatal mortality risk among the different ethnic groups in the Netherlands is of concern and we are conducting a separate study focusing on the ethnic differences in perinatal mortality.
- in the discussion section it is stated that the current perinatal registry does not contain information on smoking, however in table 2 figures are shown on percentage of heavy smoking by region. This seems contradictory.

The current perinatal registry has an option to register the item ‘severe smoking’, but this is clearly an underestimation of the true prevalence of smoking during pregnancy. So there is some information which we showed in table 2. We changed the wording in the discussion section. When we included the item ‘severe smoking’ in the adjusted model from table 3, the results did not change.

- in the discussion section it is hypothesized that a possible explanation for the unexplained regional differences might be differences in care. In the result section the authors show that there are regional differences in health services patterns (table 4). To what extent can the remaining regional differences (model II in tabel 3) be explained by the regional differences in health care factors from table 4?

It is difficult to determine to what extent the difference in health services patterns explain the differences in perinatal mortality. The mode of delivery and risk selection are interventions based on the condition of mother and child. Therefore we could not include these measures in the total regression model. The differences by region are merely an indication that difference in health services might be involved in the differences in perinatal mortality. Further research should focus on factors specific to fetal or neonatal mortality or to specific gestational age subgroups. National audit studies could inform on substandard care factors.

Minor Essential Revisions

- is there any information on the completeness of the registry with regard to early neonatal mortality?

When the perinatal data were compared to civil data in a pilot study, more fetal deaths were registered in the perinatal registries. The civil registration issues a neonatal mortality rate from 24.0 weeks gestation onwards. When this rate was compared with the perinatal mortality rate with the restriction of 24.0 weeks gestation onwards, the rate differed by around 0.2‰.

- why is probabilistic record linkage necessary, to identify infants occurring in more than one registry?

In the Netherlands no unique identifier is available to identify mothers/children occurring in more than one registry. Probabilistic medical record linkage in the best method to link files in the absence of such an identifier. It was shown in Meray et al. (ref 15) that this was a valid approach and yielded better results than a deterministic linking strategy.

- why is chosen to assign women with an unknown or invalid postal code to the province Zuid-Holland? Why is not chosen to exclude these women from the analysis?

We agree that it is a better approach to exclude these women. We now excluded women with an unknown or invalid postal code form all analyses and the results were similar.

- data presented in the last paragraph of the result section (regional differences in within the five clinical relevant risk groups) would be easier to digest when shown in a table

We incorporated an additional table with the prevalence and mortality risks of the five clinical risk groups by region (table 5).

- in table 1 after 'Utrecht' the sign '#' is typed, this seems a typo

The sign is removed from the table.

- it is unclear what is meant by two sentences on page 13: "The elevated mortality risk for children with congenital anomalies in the region north (while prevalences was similar) might
also point to differences in care shortly after birth. Late neonatal mortality showed the same regional pattern, excluding mortality differences by different care management during the first week”. Please clarify.

We included a table with the prevalence and mortality risks for the five clinical risk groups by region. It can be seen from this table that the prevalence of severe congenital anomalies is similar for all regions, but that the mortality risk for this group is higher in region North. A potential reason might be that the care shortly after birth is different per region. Extensive treatment in the first week could result in the ‘delay’ of mortality to after the first week. As the regional pattern was also observed in late neonatal mortality, this was not the case here. We changed the wording in the discussion to clarify.

**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