Author's response to reviews

Title: Maternal blood manganese level and birth weight: a MOCEH birth cohort study

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

We have revised the manuscript to meet the format of Environmental Health. Please refer to the revised manuscript. We appreciate your suggestions and work.
Dear reviewers,

We appreciate your comprehensive comments and suggestions. We find it is very helpful in upgrading our manuscript. Please refer to our responses listed below.

**Reviewer 1: Sylvaine Cordier**

**Reviewer’s report:**
No further request

**Reviewer 2: Maryse F. Bouchard**

_I am satisfied with the revisions performed, but there a few problems in this last version, mostly in the discussion._

**RESULTS**

_In Table 3, what is the justification for these Mn blood concentration categories? The lowest and highest blood Mn categories are very small: 11 and 17 women, respectively. Since there are 331 women, these groups represent 3% and 5% of women, respectively. Because the groups are so small, the AOR are extremely imprecise. It would make more sense to create groups based on the distribution of the data, such as quintiles._

As you commented, we revised the Table 3 as follows:

<table>
<thead>
<tr>
<th>Maternal blood manganese level (μg/dL)</th>
<th>No. of subjects</th>
<th>AOR†*</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12</td>
<td>11</td>
<td>5.82</td>
<td>(0.88-38.47)</td>
<td>0.068</td>
</tr>
<tr>
<td>12 – 19</td>
<td>121</td>
<td>1.50</td>
<td>(0.43-5.17)</td>
<td>0.524</td>
</tr>
<tr>
<td>20 – 27</td>
<td>145</td>
<td>1.42</td>
<td>(0.43-4.65)</td>
<td>0.566</td>
</tr>
<tr>
<td>28 – 35</td>
<td>37</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;36</td>
<td>17</td>
<td>4.34</td>
<td>(0.80-23.49)</td>
<td>0.089</td>
</tr>
</tbody>
</table>
Maternal blood manganese level (μg/dL) | No. of subjects | AOR** | 95% confidence interval | p-value
--- | --- | --- | --- | ---
<16.9 | 66 | 2.77 | (0.89-8.65) | 0.079
16.9 – <20.0 | 65 | 1.41 | (0.42-4.79) | 0.580
20.0 – <22.9 | 65 | 2.43 | (0.79-7.52) | 0.123
22.9 – <26.9 | 65 | 1.00 | - | -
>26.9 | 65 | 2.60 | (0.84-8.08) | 0.098

DISCUSSION
The reference 22 (Legleiter et al. Influence of dietary manganese on performance, lipid metabolism, and carcass composition of growing and finishing steers) is the strangest choice of reference I have ever since. It is completely inappropriate to support the statement that “the biological activity of serum and whole blood Mn is different”. Also, I am sure what “the biological activity of serum and whole blood Mn is different” actually means. Please rewrite.

As you commented, we revised discussion as follows:

Because blood Mn level in the cord blood is higher than that in maternal blood at the time of delivery [20,21] and the biological activity of serum and whole blood Mn is different [16,22], this study cannot be directly comparable to our study.

Because blood Mn level in the cord blood is higher than that in maternal blood at the time of delivery [20,21] and this study was conducted with serum, it cannot be directly comparable to our study.
The reference 23 from 1987 is not appropriate to support a statement saying that there is currently few data on Mn in relation to birth outcomes.

As you commented, we revised discussion as follows:

Many studies reported the effects of Mn deficiency in animals, but human studies have shown an association between deficiencies in Mn and poor pregnancy outcomes [23].

↓

Many studies reported the effects of Mn deficiency in animals, but human study is rare [3] to our knowledge.

Please rewrite the last sentence of the discussion “We obtained consistent results even though our study was conducted on a female population without any specific environmental or occupational source of exposure. We also found a coherent dose-response relationship between maternal Mn level and birth weight.”

Consistent with what?
What is a coherent dose-response relationship?

As you commented, we revised the last sentence of discussion as follows:

Our results confirm the non-linear relationship reported in a previous human study [14] and the association between Mn exposure and lower birth weight in animal studies [30]. We obtained consistent results even though our study was conducted on a female population without any specific environmental or occupational source of exposure. We also found a coherent dose-response relationship between maternal Mn level and birth weight.

↓

Our results confirm the non-linear relationship reported in a previous human study [14] and the association between Mn exposure and lower birth weight in animal studies [30] even though our study was conducted on a female population without any specific environmental or occupational source of exposure.

CONCLUSIONS

“These results may help to determine the reference level for Mn intake in pregnancy.” I do not agree with this because you have no way to infer anything about the level of intake that would be produce blood Mn levels associated with lower birth weight (blood Mn too low or too high).selected.

As you commented, we revised conclusions as follows:

Our study found that both extreme level of maternal Mn level was associated with lower birth weight outcome in a nonlinear fashion. These results may help to determine the reference
level for Mn intake in pregnancy.

↓

Our study found that both extreme level of maternal Mn level was associated with lower birth weight outcome in a nonlinear fashion.