Author’s response to reviews

Title: Perinatal mortality in pregnancies with omphalocele: data from the Chinese national birth defects monitoring network, 1996-2006

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Author’s response to reviews:

Dear editors and reviewers,

Thank you very much for your hard work and constructive suggestions. We have considered carefully each question and comment, and have substantially revised our manuscript after reading your insightful comments. We also have responded to all the comments one by one in this letter, and the amendments are highlighted in red in the revised manuscript. As the BioMed Central Editorial recommendations, we have used Edanz’s English language editing service to polish our wording. If you have any questions and suggestions for our study, we are welcome to receive the letter from you. Thank you very much again.

We hope that this revised version of the manuscript is now acceptable for publication in your journal.

We are looking forward to hearing from you soon.

Yours sincerely,

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Reviewer: 1

Comments to the Author

Page 4: As a linguistic error, “death in utero” was corrected by “die in utero”; “at the earlier gestation weeks” was corrected by “at the earlier gestational weeks”.

Answer: Thank you very much for your good suggestions. We have used Edanz’s English language editing service, and corrections have been made in the Background in the revision of the manuscript (Page 4, line 87-88).

Page 5: MER: You are comparing two different entities, i.e. non-isolated should be vs. isolated, prenatal detected should be vs. postnatal detected.

Answer: Thank you very much for your good suggestion. We are sorry that we did not clarify the aim of our study clearly. We have revised the aim of this study in the revision of the manuscript as your suggestions (Page 5, line 95-98).

Page 5: MER: why not an absolute number?

Answer: Thank you very much for your insightful comments. Because the number of births in some of the sampled surveillance hospitals had declined, we increased the number of hospitals that were selected from neighboring counties to monitor a sufficient amount of births to ensure a representative sampled population.

In addition, some of the member hospitals were replaced by other neighboring hospitals because of reorganization of their medical services. Therefore, the number of hospitals over the study period changed in our analysis, which was not an absolute number. We have added these explanations into the revision of the manuscript (Page 9, line 179-185).

Page 5: MER: better: recognized

Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 5, line 110).

Page 6: MR: better: after which

Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 6, line 115).

Page 6: MER: better: staff

Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 6, line 115).

Page 6: MR: better: these

Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 6, line 115).

Page 6: MR: better: controlled

Answer: Thank you. Corrections have been made in the Methods/Ascertainment
of cases in the revision of the manuscript (Page 6, line 116).

Page 6: MR: better: above mentioned
Answer: Thank you. We have used Edanz’s English language editing service, and corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 6, line 116).

Page 6: MER: “also” was deleted.
Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 6, line 119).

Page 6: MR: better: participating
Answer: Thank you. We have used Edanz’s English language editing service, and corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 6, line 119).

Page 6: MER: When was the consent done??? What did the consent include???
Answer: Thank you very much for your good questions. The monitored population in our network only included births with 28 gestational weeks or more who were delivered in the member hospitals. The parents of these newborns were informed before they were discharged from the hospital. The consent mainly included the aims and significance of monitoring birth defects. We have added these description into the revision of the manuscript (Page 6, line119-121).

Page 6: MR: better: -s
Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 6, line 124).

Page 6: MR: better: is
Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 6, line 124).

Page 6: MR: better: surrounded
Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 6, line 124).

Page 6: MER: better add: …based on the …
Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 6, line 128).

Page 6: MER: Where the tables including these parameters???
Answer: Thank you very much for your good questions. In our study, we have analyzed the association between perinatal mortality of omphaloceles and gestational age and birthweight (please see Table 3). Therefore, the variables of gestational age and birthweight were considered in our analysis. Detailed analyses were shown in the Results of the revised manuscript (Page 11,
paragraph 2). The two variables have been revised in the revision of the manuscript (Page 7, line 135-137).

Page 6: MCR: This is not equal to your classification in table 2
Answer: Thank you very much for your good questions. In our preliminary analysis, we divided maternal age into six subgroups, including <20 years old, 20-24 years old, 25-29 years old, 30-34 years old, 35-39 years old, and #40 years old. Group of <20 years was combined into group of 20-24 years and group of #40 years was also combined into group of 35-39 years due to the small number of cases in these groups, which was noted in the footnote of Table 2. Therefore, only four maternal age groups were shown in Table 2. As your kind suggestions, we have revised the maternal age groups in accordance with the classification in Table 2 (Page 7, line 133-134).

Page 6: MER: divided
Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 7, line 135).

Page 7: This classification did not appear in a table or result, if it has no purpose in your trial, then you may remove it (MCR)
Answer: Thank you very much for your insightful comments. In our study, we have analyzed the association between perinatal mortality of omphaloceles and gestational age and birthweight. In our analysis, gestational age was divided into 28–36 weeks and 37–42 weeks, and birthweight was grouped into <2500 g and #2500 g (please see Table 3). Detailed analyses were shown in Results of the revised manuscript (Page 11, Paragraph 2). We have revised the description of these variables in the revision of the manuscript (Page 7, line 135-137).

Page 7: MR: better: is defined as
Answer: Thank you. After reviewing carefully, we have deleted these contents in accordance with our analysis in the revision of the manuscript.

Page 7: better: -s MR
Answer: Thank you. We have used Edanz’s English language editing service, and corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 7, line 137).

Page 7: MR: better: which
Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 7, line 137).

Page 7: MR: better: or structural abnormalities
Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 7, line 138).

Page 7: MR: better: …not related to…
Answer: Thank you. Corrections have been made in the Methods/Ascertainment
of cases in the revision of the manuscript (Page 7, line 139-140).

Page 7: MER: gestational age
Answer: Thank you. Corrections have been made in the Methods/Ascertainment of cases in the revision of the manuscript (Page 7, line 144).

Page 7: MER: routinely evaluated
Answer: Thank you. Corrections have been made in the Methods/Data quality management in the revision of the manuscript (Page 7, line 149).

Page 8: MER: Cochrane
Answer: Thank you. After in-depth discussion with some statisticians, it is optimal to use the Cochran-Armitage Trend Test to assess the trend of mortality of omphalocele over time, not the Cochrane-Armitage Trend Test.

Page 8: MR: better: while
Answer: Thank you. We have used Edanz’s English language editing service, and corrections have been made in the Results in the revision of the manuscript (Page 9, line 192).

Page 9: MER: most commonly
Answer: Thank you. Corrections have been made in the Results in the revision of the manuscript (Page 9, line 193).

Page 10: MER: did
Answer: Thank you. Corrections have been made in the Results in the revision of the manuscript (Page 10, line 217).

Page 10: These abbrev. appear for the first time
Answer: Thank you. We have used Edanz’s English language editing service, and these abbreviations were firstly presented in the Methods/Ascertainment of cases (Page 7, line 143-145).

Page 10: MER: …was of no…
Answer: Thank you. We have used Edanz’s English language editing service, and corrections have been made in the Results in the revision of the manuscript (Page 11, line 226).

Page 10: MER: Sentence makes more sense like this
Answer: Thank you. Corrections have been made in the Results in the revision of the manuscript (Page 11, line 236-237).

Page 11: MER: had
Answer: Thank you. After reviewing carefully and according to another reviewer’s comments, we have deleted these contents to shorten the discussion of the revised manuscript.
Thank you. After reviewing carefully and according to another reviewer’s comments, we have deleted these contents to shorten the discussion of the revised manuscript.

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Thank you. Corrections have been made in the Discussion in the revision of the manuscript (Page 12, line 254).

Thank you. After reviewing carefully and according to another reviewer’s comments, we have deleted these contents to shorten the discussion of the revised manuscript.

Thank you. After reviewing carefully and according to another reviewer’s comments, we have deleted these contents to shorten the discussion of the revised manuscript.

Thank you. After reviewing carefully and according to another reviewer’s comments, we have deleted these contents to shorten the discussion of the revised manuscript.

Thank you. Corrections have been made in the Discussion in the revision of the manuscript (Page 12, line 260).

Thank you. Corrections have been made in the Discussion in the revision of the manuscript (Page 12, line 262).
Page 14: Should be rephrased completely (MCR) !!!
Answer: Thank you very much for your insight comments. We are so sorry that our conclusions caused some confusion in this manuscript. After discussing with some birth defects epidemiologists, we have revised the conclusions in the revision of the manuscript. Detailed descriptions have been seen in the Conclusion of the revised manuscript (Page 14, line 293-298).

Page 15: MER: missing abbreviations: LFD and ENND.
Answer: Thank you. We have added the abbreviations of LED and ENND into the revision of the manuscript. Please see the Abbreviations of the revised manuscript (Page 14, line 301-302).

Reviewer: 2
Comments to the Author
On p 5, in discussing ascertainment, what proportion of all births in China are covered by the registry? Are there any aspects to selection of cases based on included hospitals or severity of fetal condition?

The CBDMN has developed hospital-based surveillance systems nationwide over the past 20 years. In the CBDMN, all births with 28 gestational weeks or more who were delivered in the member hospitals were monitored, including live births, stillbirths and terminations of pregnancy. And all member hospitals were involved in our study. The selection of cases did not base on the included hospitals or the severity of fetal condition.

On p 6, how are diagnoses validated? Most especially, how are cases of gastroschisis or limb-body-wall defect differentiated from omphalocele?
Answer: Thank you very much for your good questions. In the CBDMN, we have developed the Birth Defects Diagnosing Regulation. Following this regulation, all member hospitals made the diagnosis for all kinds of congenital malformations. Omphaloceles were diagnosed by physical examination by trained obstetric and pediatric clinicians. The cases were confirmed by documentation of the postnatal diagnosis and narrative descriptions of abnormalities in the medical records. Cases diagnosed by prenatal ultrasonography were also confirmed by health professionals according to the postnatal records after delivery. For pregnancies ending in stillbirth or elective termination, the autopsy report provided additional information to confirm the diagnosis. We have revised the diagnosis validation in the revision of the manuscript (Page 5, line 110; Page 6, line 111-113 & line 117-119).
Abdominal wall defects are major abnormalities easily identifiable at birth. According to the International Clearinghouse for Birth Defects Monitoring Systems, omphalocele was defined as a midline abdominal wall defect limited to an open umbilical cord. The viscera herniates into the base of the umbilical cord and is surrounded by the peritoneum and amniotic membrane. Gastroscisis is a paraumbilical defect of the anterior abdominal wall without a covering membrane, usually to the right of the umbilical cord, associated with evisceration of abdominal organs. Limb-body-wall defect is a severe congenital disorder characterized by very severe limb defects and anterior body wall defects. Based on the above mentioned definitions, the trained obstetric and pediatric clinicians in our member hospitals can easily differentiate gastroscisis or limb-body-wall defect from omphalocele for cases at birth. Cases of gastroscisis or limb-body-wall were excluded from our analysis. In addition, for pregnancies ending in stillbirth or elective termination, due to the false-positive rate of prenatal ultrasound and the missing information on autopsy report some gastroscisis or other abdominal wall defects may be misclassified as omphalocele. We have added the limitation into the revision of the manuscript (Page13, line282-286). However, according to the published report the rate of the misclassification was very low (Hwang PJ, Kousseff BG. 2004. Omphalocele and gastroscisis: an 18-year review study. Genet Med 6(4):232-6.). Also, in the member hospitals of the CBDMN all ultrasound clinicians are trained using a standardized guideline. Therefore, the rate of the misclassification was also very low in our study.

Also on p 6, in considering variables for analysis, it would be interesting to also include whether the mother was part of the floating population, as well as gravidity and plurality.

Answer: Thank you very much for your good questions. We also agree that it would be interesting in our analysis to include whether the mother was part of the floating population, as well as gravidity and plurality. However, we did not investigate the above mentioned variables during the study period in our analysis. Therefore, we cannot gather related data on these variables in this study. In the following monitoring network, we will include these variables into our birth defects register system and we can analyze these variables in the future study.

On p 7, in the section on data quality, tell the reader something specific as to how this applies to the cases in this study. How many of these cases were validated, for example?

Answer: Thank you very much for your insightful comments. In the CBDMN, the Data quality management (DQM) aimed to check the data collection, data reporting, diagnosis of defects, and obstetric and pediatric medical records following the surveillance manual to improve the accuracy, comparability, completeness, and timeliness of registered data. The DQM was a routine work and included three levels (county level, provincial level, and national level). The county level DQM was required to examine all member hospitals quarterly. Therefore, almost births affected by congenital anomalies, especially major structural malformations like omphalocele, can be identified by the county level
DQM. For DQM at the provincial and national level, only a small number of cases were identified and these cases were mostly minor malformations, such as patent foramen ovale, haemangioma, undescended testicle. The under-reporting rate of live births or malformations needed to be no greater than 1%, and errors or missing information on the report form had to be no greater than 1%. At each level, a panel of senior health professionals was committing to evaluate the completeness, accuracy and timeliness of data. During the study period, there was no any underreported omphalocele found by the provincial and national level DQM. In our revised manuscript, we have given some specific description on the DQM. Please see the revision of manuscript (Page 7, line 149-154; Page 8, line 155-160).

On p 8, explain more clearly why multinomial logistic regression was used. Also on this page, a good place to explain why data are only through September 2006, and perhaps also whether reporting was continuous over the study period, or more cases collected in later years of the study period. Did the prevalence of omphalocele change over the study period?

Answer: Thank you very much for your good questions. We have explained more detailly why multinomial logistic regression was used in the revision of the manuscript (Page 8, line 169-173).

The CBDMN was one part of the Chinese Maternal and Child Health Monitoring Network. With the decline of the maternal mortality rate, the network was required to increase the sample size through enlarging the member hospitals to cover enough monitored population. Since September 2006, the number of the member hospitals has almost doubled. Therefore, to ensure the comparability of registered data from the member hospitals, our study period was confined to January 1996 through September 2006. During the study period, because the number of births in some of the sampled surveillance hospitals had declined, we increased the number of hospitals selected from the neighboring counties to monitor a sufficient amount of births to ensure a representative sampled population. In addition, some of the member hospitals were replaced by other neighboring hospitals due to reorganization of their medical services. Therefore, the number of hospitals over the study period in our analysis changed. The prevalence of omphalocele ranged from 1.1 to 1.9 per 10,000 births and there was no significant statistical difference ($\chi^2=0.130$, $P>0.05$). We have added these explanations into the revision of the manuscript (Page 9, line 177-185).

On p 9, first line, what does ‘most prevent in . . .’ mean? What is an uptrend or downtrend? The observation of different patterns for LFDR and ENNDR suggests some possible classification bias based on whether a case was considered a live birth.

Answer: Thank you very much for your good questions. This referred to the proportion of associated anomalies with omphalocele. In our analysis, although cleft lip with or without cleft palate or cleft palate was the most commonly associated anomalies with omphalocele, the number over study period was very small (n=45). Therefore, we could not analyze the trend of the associated anomalies with omphalocele.
In our analysis, LFDR was calculated by the number of stillbirths and terminations of pregnancy divided by the total number of births with omphalocele and ENNDR was the number of neonatal death within the first 7 days after birth divided by the total number of births with omphalocele. The births as the denominator included live births, stillbirths, and terminations of pregnancy.

Beginning on p 11, the discussion is not well organized. The references to other literature are drawn out and could be more easily summarized, perhaps in .5 pages rather than 2 full pages. Perhaps a table comparing these results to this study would be helpful.

Answer: Thank you very much for your kind suggestions. We have shortened the discussion of the revised manuscript. Please see the revision of the manuscript (Page12). We are very sorry that we did not use a table as your suggestions to compare these results because using a table in the discussion was not fit for the whole style of the journal of BMC Pediatrics.

On p 14, the authors could discuss other potential limitations. For example, is this study truly population-based, since it focuses on selected hospitals rather than all deliveries in a region? Is the diagnosis made uniformly across all hospitals in the registry?

Answer: Thank you very much for your kind suggestions. Population-based surveillance system covers the entire birth population over a specific area and thus, can obtain more reliable prevalence estimates of birth defects. However, it needs a large amount of resources to operate compared to the hospital-based surveillance system. The hospital-based surveillance program monitors neonates born in the network hospitals. This program is easy to implement and can usually obtain high-quality diagnoses. However, the surveillance data collected by hospital-based systems represent only the birth defects information in the selected areas. The hospital-based samples may have introduced referral bias. The hospital-based surveillance model can be adopted by developing countries that have limited resources. With the growth of the economy and development of healthcare services worldwide, it is becoming a necessity to build population-based birth defects surveillance systems which are supplement to hospital-based surveillance systems. However, because of the wide geographic coverage, consistent case ascertainment, and the large sample size, the CBDMN data used in our study were reliable. We have added theses limitations into the revision of manuscript (Page 14, line 287-290).

In our monitoring system, we have established the Birth Defects Diagnosing Guideline. The physicians/clinicians in all member hospitals must follow the guideline to diagnose the birth defects. What's more, all cases are uniformly verified by CBDMN professionals from county-level, provincial-level and national-level following the Birth Defects Diagnosing Guideline.

Turning to the tables, in Table 1 since the data are presented as percents, a single decimal place is sufficient, while column headers could be spelled out rather than abbreviated. Was any trend over time observed?
Thank you very much for your kind suggestions. As you suggested, we have used a single decimal place in Table 1. And we have revised the column headers in the revision of the manuscript. The trend over time was analyzed in the revision of manuscript. Please see Page10, line206-208.

In Table 2 or 3, it would be interesting to see if there are differences in mortality by level of perinatal services available at the hospital of birth, as well as by complexity of associated birth defects if any. Table 3 should also show the results for perinatal mortality - and it might be interesting to include gestational age using the fetuses at risk approach.

Thank you very much for your insightful comments. In our study, we have investigated the association with mortality by level of perinatal services available at the hospital of birth. In China, due to the imbalance of the social and economic development in the different geographic locations, there is a disparity of perinatal services available in the hospital among coastal areas, inland areas, and remote areas. Generally speaking, the perinatal services available at the hospital of birth in the coastal areas are better than of the inland areas and the remote areas. In Table 2, we analyzed the association with perinatal death of omphalocle by geographical locations, showing that fetuses or neonates with omphalocele who were located in inland areas had 1.56-fold or 1.72-fold higher mortality than that of coastal areas (adjusted odds ratio (AOR):1.56, 95% CI:1.09-2.24; AOR:1.72, 95% CI:1.03-2.85, respectively) and late fetal death rate or early neonatal death rate in remote areas seems to be slightly higher compared with coastal areas (AOR:1.07, 95% CI:0.73-1.57; AOR:1.53, 95% CI:0.91-2.59, respectively), though there was no significantly difference.

We agree that it would be interesting to see if there are differences in mortality by complexity of associated birth defects if any. In the following study, we will collect more cases to analyze specially the association among the perinatal mortality of omphalocele and the complexity of associated congenital anomalies.

As your suggestions, we have added the results of perinatal mortality in Table 3 and also in Table 2 in the revision of the manuscript. In our analysis, we have investigated the association with perinatal mortality of omphalocle by gestational age. Please see the Table 3.