Author's response to reviews

Title: The geographical and urban-rural disparities in the total prevalence of neural tube defects and its subtypes during 2006-2008 in China: a study on the hospital-based birth defects surveillance system

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

Thank you very much for prolonging the time for us to revise the manuscript. Thanks for the reviews’ useful suggestions. In this revised manuscript, we focused on geographical and urban-rural disparities in total prevalence of NTDs between 2006 and 2008 in China. We made the widely revisions after studying the reviewers’ comments carefully. The modified text in our article is marked by blue colour. We obtained each co-author’s consent for our modified manuscript. We also have responded to all the comments one by one in this letter. We have asked native speaker to help us copyediting the English. We hope the revised version is better in both content and language and therefore has a better chance of being accepted by your journal.

Should you find our response ambiguous or improper, please feel free to contact us.

Thank you for your time and efforts in dealing with our manuscript.

Yours Sincerely

Juan Liang.
Response to reviewer's comments:

Reviewer: Saeed Dastfiri
Reviewer’s report:
1) The aim of the study is not clear, this needs to be clarified.
   Answer: Thanks. We agree that the former version of our manuscript is not clear enough about its objective. According to three reviewers’ suggestion, our article’s objective has been refined. This revised manuscript focus on the geographical and urban-rural disparity in the total prevalence of NTDs at any gestational weeks in China with the purpose of providing new insights for prevention and management. So the content of our article has been also refined according to the objective. The descriptions of prevalence of NTDs more than 28 weeks gestational age and the variation of maternal age-specific prevalence of NTDs have been deleted so as to suit our refined objective.

2) More details are needed about the setting of the study population.(i.e. coverage? socio-economic status? reproductive history? etc)
   Answer: Thanks for your good suggestion. The coverage and socio-economic status of the study population has been added in the data source of the methods section. Please seen our modified manuscript. However, we do not have a way to add the reproductive history of 116 counties or districts. Because we do not have the accurate data about the number of live births in these counties or districts from our hospital-based monitoring system. The main reasons about the birth number in these counties or districts increasing to 840,341 in 2008 from 641,789 in 2006 are the increasing hospitalized delivery rate and the increasing proportion of births delivered in the county-high level hospitals.

3) The conclusion does not seen to be indicative enough. Authors need to include/add some more implication of this study for the study areas and similar populations. It’s not enough to suggest intervention measures without clear justifications based on the findings.
   Answer: The suggestion is very useful. As the contents in our study have been widely modified according to the reviewers’ suggestions, so we also have modified the section of conclusion. Please see the revised manuscript.

4) It is unclear what the authors mean by PR when they say it is prevalence ratio? What dose prevalence ratio mean? Is that prevalence rate? These should be clearly be defined and clarified in the “methods”.
   Answer: We are sorry that we do not clarify the “prevalence ratio” in the methods. We have clarified in the “methods” as your suggestion.
   The prevalence rate or prevalence proportion is equal to the number of NTDs at any gestational weeks divided by the number of birth or terminations of pregnancy for fetal anomaly (TOPFA) regardless of gestational weeks. However, the number of total births or TOPFA at any GA cannot be obtained from the CBDMN. So in our study, the prevalence of NTD is calculated by the number of NTDs at any gestational weeks as the numerator and the
number of birth more than or equal to 28 gestational weeks as the denominator. The prevalence of NTD in our study is not accurately the prevalence rate or prevalence proportion, so we use the prevalence ratio.

5) I do not see any ‘key words’ in the abstract section.
Answer: This is our negligence. We have added the key words.

6) Authors need to include more details about the diagnosis and detection procedures of birth defects in the study setting.
Answer: Thanks for your suggestion. More details about the diagnosis and detection procedures of birth defects in the study setting. A three level (county, province, and central) surveillance network and corresponding expert groups were established to undertake data collection. Every neonate or stillbirth is immediately examined after birth by trained healthcare professionals to screen for birth defects. For cases of abnormalities diagnosed by prenatal diagnosis and terminated before 28 weeks GA was reconfirmed after birth. At each level of surveillance network, the expert group usually composed of pediatricians, obstetricians, and ultrasound specialists is in charge of confirming the cases’ diagnosis. If the case cannot be confirmed, the expert group at the provincial level is responsible for its diagnosis by reviewing the case’s medical record or its photos. At the national level, annual expert seminar is hold to diagnose the unknown cases also by using a review of medical records and photos. If the case cannot be clearly diagnosed, it will be excluded from the system.
Reviewer’s report:
1) It would be helpful if the authors used the usual term in the field of congenital anomalies, total prevalence, when referring to their data on prevalence of NTD. For example, the title “…prevalence of neural tube defects and its subtypes at any gestational age” is a bit cryptic, at least on first reading. The authors could use the term total prevalence or even simply prevalence in the title and then explain in the text that in this paper they provide data on total prevalence of NTD in that they include all cases and not just those after 28 weeks of gestation, as previously reported.

Answer: Good suggestion. We have done as the suggestion.

2) It would also be clearer to speak of live births, still births and TOPFA instead of “…malformation that are born or induced” (cf. second paragraph in the Methods section).

Answer: Good suggestion. We have done as the suggestion.

3) In the Introduction, the authors note that “the monitoring subjects of most birth defects surveillance system in the world does not include cases less than 20 weeks”. However, the EUROCAT network of European Registries of Congenital Anomalies provides data on prevalence of NTD including TOPFA regardless of gestational age (see Greenlees et al, Birth Defects Research 2011 and the EUROCAT website: http://www.eurocat-network.eu/). Total prevalence of NTD is also one of the public health indicators for congenital anomalies proposed by EUROCAT (Khoshnood et al, Birth Defects Research 2011).

Answer: We have modified this sentence and add the reference.

4) I think the study / paper would benefit from a simpler statistical analysis. It seems to be that this is a case of “more is less”. The authors tested several two-way interactions between maternal age, rural/urban, south/north, and time which complicates both the analysis and presentation of results; especially since given the large sample size, it is not hard to find significant interactions.

Answer: Good suggestion. We have modified the statistical model, in which we select one interaction term (Region*Residential area). The statistical results look more clearly than before.

5) At times, it also seems that the way they presented the results was not quite right – for example presenting the intercept (beta0) as the “basic risk of NTDs” is not quite right – the intercept in fact represents (can be used to calculate) the prevalence rate for the reference group. The authors also seem to report “main effects” in the presence of significant interactions, which is not standard practice.

Answer: You are right. We asked the statistical expert and modified the statistical methods in this article.

6) In any case, I am not really sure that the interactions add much to the paper. They are indeed statistically significant but I don’t really think that from a public health point of view, they are very helpful for informing policy interventions. Perhaps the only one worth keeping is the rural-region one, in order to underscore the particularly high prevalence of NTD in the rural North
7) Table 2 is hard to read and needs to be revised (to be honest it actually reads more like an output file from a statistical software package than a table for readers of a journal). There is no need to give both the coefficients (betas) and their exponentiated values (exp (b)). The former can be omitted and the latter presented as prevalence rate ratios (PRR) in the table. The chi-square values are also not really needed. Instead, a confidence interval for the PRR would be more helpful. The list of variables can also be made more explicit (e.g., year instead of “t” or region instead of “Rg”).

Answer: It’s a good suggestion. Done as the suggestion.

8) The manuscript needs quite a bit of editing to clarify certain statements and correct typographical or other errors. A few examples of statements that need to be re-phrased or otherwise revised are:

Abstract
“The association between PR of different subtypes and maternal age was different after removing the impact of region and rural-urban”.

Answer: Because the content about variation in maternal age-specific prevalence of NTDs has been removed from our modified manuscript, so we also have deleted this sentence.

Introduction
“… and nutritional factors have been found to develop the measures for the prevention of NTDs.”

Answer: We have modified this sentence, please see the introduction section.

“it seems to be that it does not be the most serious problem.”

Answer: We have modified this sentence, please see the introduction section.

“The study will show the prevalence of NTDs at any gestational weeks by removing the impact of prenatal diagnosis…”

Answer: We have deleted this sentence so as to avoid misunderstanding.

Methods
“..the monitoring subjects of most birth defects surveillance system in the world does not include cases less than 20 weeks”

Answer: We have modified this sentence.
Reviewer: Marilyn Felkner

1) Lines 21, 24, 27, 34: It would be nice to know more specifics about the credentials and training of the various staff who are involved, especially how they differ from one another ("Experts in relevant medical department" "experts in the member hospitals" and "the expert in higher-level hospitals," "staff specifically assigned," "specialized staff."). Are they physicians, nurses, other types of health care providers, public health outreach workers, statisticians, data entry clerks? Are they specialists? Did they have specific training related to this project?

**Answer:** We are very sorry for our poor English expression. We have modified it. You know that a three level (county, province, and central) surveillance network was established to undertake data collection and case confirmation. In each member hospital, the trained healthcare professionals are responsible for examining every neonate or stillbirth to screen for birth defects. The experts group at county-level and provincial-level surveillance network, usually composed of pediatricians, obstetricians, and ultrasound specialists, is responsible for confirmation of cases' diagnosis. The staff in change of birth defect monitoring, usually the nurse in the member hospital, is responsible for collecting the information about the mothers and filling the "Birth Number Register Form" and "Birth Defect Register form".

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Abstract

2) line 6: years should be 2006-2008, not 2008-2008

**Answer:** We have modified it.

3) line 16: larger, not lager

**Answer:** We have modified it.

Methods

4) Line 68: Pearson chi square, not Person

**Answer:** We have modified it.

Results

5) Line 13: Use -, not ~ between confidence limits

**Answer:** We have modified it.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

Background

6) line 8: The statement “…many risk factors, such as genetic, environmental and nutritional factors…” has only four citations. Two of the cited articles do not deal with NTD risk factors. The Canfield article focuses on birth defects other than NTDs and the Milunsky article is about screening results rather than risk factors. A more thorough literature review is needed to support a statement on genetic, environmental, and nutritional factors.

**Answer:** We have reviewed many literatures about the risk factors of NTD. For the sake of simplicity, we have added 4 references about the summary of genetic, environmental, and nutritional factors of NTD.
Methods

7) Line 6: The authors state that the CBDMN covers “county-level-higher hospitals.” Please address if there are birth sites that are not included in the network such as smaller than county-level hospitals, birthing centers and home births. If there are, explain the rationale for not including them in the study and, in the Discussion, describe what impact the absence of these data have on the study outcome.

Answer: This is a good question. As we known, the diagnosis of birth defects is a difficult thing. In China, only the county-level-higher hospitals have the ability to diagnose the birth defects. The county_lower-level hospitals or birthing centers are impossible to correctly diagnose the birth defects. The CBDMN is hospital-based, so it covers “county-level-higher hospitals.” However, it is possible that hospital-based samples may introduce referral bias. Because there is about a 15% proportion of births delivered in the hospitals at the county level or lower. We have discussed the impact of the absence of these data on the total prevalence of NTDs. Please see the discussion section in our modified manuscript.

8) Lines 11, 12: “The monitoring subject in the CBDMN were all live births and stillbirths more than or equal to 28 week gestation age…” This seems to contradict the study’s claim to detecting birth defects at all gestational ages. There is no mention of the investigators’ method for ascertaining birth defects among fetuses less than 28 weeks.

Answer: Before 2006, the monitoring subject in the CBDMN were all live births and stillbirths more than or equal to 28 week gestation age. But after 2006, all cases with some kinds of birth defects (e.g. NTDs, congenital heart defects, acromphalus, gastroschisis, limb reduction defects, etc.) regardless of gestational ages should been registered in the CBDMN. However, the CBDMN do not collect the number of all birth or stillbirth less than 28 week gestation age. So we think that is not self-contradictory. As for the method for ascertaining birth defects among fetuses less than 28 weeks, we have added it in the methods section.

9) Line 16: the authors state that the revised monitoring program was for “cases with major lethal malformation.” Please clarify because this would not include many cases of spina bifida, which are not typically lethal.

Answer: We are very sorry. The statement “Cases with major lethal malformation.” is our clerical error. The right statement is ‘Cases with major malformation’. The major malformation mainly refers to NTDs, congenital heart defects, acromphalus, gastroschisis, limb reduction defects. We have modified it.

10) Line 20: The methods of surveillance for and ascertainment of NTDs prior to 28 weeks gestation must be included. The authors state that “every neonate is immediately examined after birth” but in the background (line 18/19) the authors explained that prior to 28 weeks most NTDs are terminated. Were all terminated fetuses also examined?

Answer: All terminated fetuses should been examined by the trained healthcare professionals. Generally speaking, any cases of abnormalities diagnosed by prenatal diagnosis and terminated before 28 weeks, GA should been reconfirmed after birth. We have modified the statement about ascertainment of NTDs prior to 28 weeks gestation.
11) Line 37: I do not understand what a “statistical standard of NTDS” means. It seems to me that the ICBDSR would establish a diagnostic standard.
Answer: Accurately, the ICBDSR has established a reporting standard for NTDs. For example, if the cases affected with anencephaly and spina bifida, in the statistics, we count this case as anencephaly, instead of spina bifida. If the cases affected with spina bifida and encephalocele, in the statistics, we count this case as spina bifida, instead of encephalocele. So we call this reporting standard as statistical standard.

12) Line 49/50: Please explain the differences in provinces/autonomous regions/municipalities. These would be overlapping jurisdictions in the U.S.
Answer: There are 22 provinces, 5 autonomous regions and 4 municipalities in mainland of China. In fact, the autonomous regions and municipalities are the same administrative level with the provinces. So that is not overlapping.

13) Lines 55/56: Please define urban and rural using population numbers or some other objective standard.
Answer: The society in China is a dual society. There is about 50% of the population living in the urban, as well as 50% of the population live in rural areas. There is a huge difference in the socio-economic development, culture, as well as the population health status, between urban and rural areas. So the analysis of health disparity between urban and rural areas is full practical significance.
But we are not very sure about your suggestion’s meaning. Could you please explain it? We feel so sorry.

14) The number of results presented in this paper is overwhelming obscuring the main the study question. It would be helpful to present the text results in the same order as the tables with prevalence rates by region, by urban/rural, and by province in the first paragraph and prevalence rate ratios in the same order in the second paragraph.
Answer: This is a good suggestion.

15) Lines 5-11: If, as stated in the explanatory letter, the objective is to examine geographic differences, comparisons between all gestational ages and #28 weeks and trends over time should be omitted from this paper. Their previously published paper can be cited for information on gestational age differences if relevant.
Answer: This is a good suggestion. We have done as your suggestion. In our revised manuscript, we focus on the geographic and urban-rural differences, and the comparisons between all gestational ages and #28 weeks and trends over time have been deleted from this paper.

16) Lines 41-51 Treating maternal age as a main variable distracts from the study question. Maternal age should be examined and reported only as a confounder and or effect modifier of geographic distribution. This section should be rewritten accordingly.
Answer: This is a good suggestion. We have done as your suggestion.
Discussion

17) Lines 1, 2: Omit discussion of differences in all ages vs. # 28 weeks.
   Answer: Done as the suggestion.

18) Lines 8-11: Omit discussion of maternal age as a main variable.
   Answer: Done as the suggestion.

19) Lines 12-34: Omit. This presumably would have been covered in the authors’ previously published paper and is not germane to the current study question. Once the gestational age has been defined in the methods, it merits little further mention.
   Answer: Done as the suggestion.

20) Lines 35-60: This should be the most important part of the article. The authors cite 4 articles to cover NTD risk factors Vitamin B, cigarette smoke, drinking, taking antipyretic drugs and antibiotics. There are hundreds of articles on NTD risk factors. The authors should do a thorough literature review of NTD risk factors, select the risk factors that are most relevant to geographic disparities in China, and discuss these selected risk factors and their relation to their findings in depth.
   Answer: It’s a very useful suggestion. We have done a thorough literature review of NTD risk factors, and discussed the selected risk factors (including residents’ lifestyle, hazardous environmental exposure, and the vitamin supplementation). Please see our revised manuscript in details.

21) 61-64: The authors have one citation for education level, health awareness, access to preconception care, and periconceptional nutrition. Their importance as NTD risk factors should be covered more thoroughly.
   Answer: It’s a very useful suggestion. We have modified this section. We have discussed the different in residents’ education level, health awareness, and maternal nutritional status between urban and rural areas. However, there are little published articles about the NTD risk factors’ distribution in urban and rural areas.

22) Lines 79-92: Discussion of maternal age is outside the scope of this study.
   Answer: We have deleted the discussion of maternal age from our study.

23) The limitations of ascertaining NTDs at less than 28 weeks should be discussed. At what GA are NTDs not discernible? Would this ascertainment vary depending on the available technology or variable access to prenatal care? How would the resulting differences in case ascertainment impact the PRs?
   Answer: It’s a very useful suggestion. We have added this limitation in the discussion section. Please see the discussion section.

24) Table 1 is very nicely organized. To keep the focus on geographic disparities, omit maternal age from Table 1.
   Answer: Done as the suggestion.
25) Table 2 should be organized similarly to Table 1. The table should be understood without referring to the text. So use plain language rather than statistical symbols to label column headings. The variables should be clearly named. The referent group should be identified. Confidence intervals are preferable, but p-values are acceptable. The beta and chi square can be omitted. Omit maternal age as a main variable. Adjusting for age, as is indicated in the footnote, is sufficient.

**Answer:** Good suggestion. Done as the suggestion.

Figures

26) Omit Figure 1. It is unrelated to the study question for this paper.

**Answer:** Done as the suggestion.

27) Figure 2. Very nice way to present these data. However, in gray shades, it is very difficult to make that number of distinctions. If the publication will not be in color, collapse some of the categories.

**Answer:** Your suggestion is good. But we would like to show this figure in color, because we think it is clearer that the different NTD prevalence is shown by using different color. If the publication in this journal will not be in color, we will accept your suggestion.