PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Adverse birth outcomes in Guangdong province, China, 2014-2017: a spatio-temporal analysis of 2.9 million births
AUTHORS	Miao, Huazhang; Li, Bing; Li, Wu; Yao, Fei; Chen, Yuliang; Chen, Ruyin; Lin, Jiumin; Wu, Yuntao; Guo, Pi; Zhao, Qingguo

VERSION 1 – REVIEW

REVIEWER	Oyelola Adegboye, PhD Australian Institute of Tropical Health & Medicine, James Cook University
REVIEW RETURNED	16-May-2019

| GENERAL COMMENTS | This is a well written and well detailed manuscript. The article presents descriptive findings using a large births data in Guangdong province of China. However, I have three major comments regarding the general introduction and statistical techniques used.
Major comments:
1.   The introduction lacks relevant literature on PTB, LBW and SGA situation in the study region or even China in general. It will be good to know the current incidence/prevalence of these birth outcomes in China
2.   One of your objectives is to analysed regional differences of PTB, LBW and SGA between the Pearl River Delta and Non-Pearl River Delta regions. However, there is did not mention the statistical method you will use to make inference regarding this objective in the "data analysis" section. You also mentioned that "All statistical tests were 2-tailed. P-value less than 0.05 were considered to be statistically significant." There is no single result presented using a statistical inference in this study.
3.   In the same vein, the authors mentioned on page 7 line 24-26 that "We mapped the spatial distributions of rates for the adverse birth outcomes to investigate the spatial distributions pattern of the birth outcomes through 2014 to 2017." How did you confirm that there are spatial heterogeneity of birth outcomes?

Minor comment:
4.   Page 4 line 16: Insert space between 10th and percentile
5.   Page 4 line 16-17: "…weight falls below the 10th percentile by sex and gestational week of all singleton live Births". By this statement do you mean all singleton live births in a region?
6.   Page 7 line 44-49: These statements does not read well and the 27% is not necessarily large if you compare it to 26% in 2014 and 25% in 2017.
You may rewrite as:
"There were a total of 2,917,098 births in Guangdong province during the study period, 1,553,948 (53.27%) were boys. |

Approximately 22% (627,146) babies were born in 2015, which is the lowest population of all births between 2014 and 2017."

7.   Page 8 line 5-41: The results does not present any statistical inference to support the differences observed or not observed. Adding a statistical test to Table 2 will improve the validity of your results and give credence to the presentation.

8.   Page 9: Add a spatial heterogeneity test to confirm the spatial variability of each birth outcomes.

9.   The discussion is well written, however, it is essential that the authors discuss in depth the reasons for the differences observed between the regions and seasons.

REVIEWER	Jeanette Stingone Columbia University, USA
REVIEW RETURNED	20-May-2019

GENERAL COMMENTS	The authors conducted a descriptive analysis examining the patterns of adverse birth outcomes in Guangdong China. It is unclear what this study adds to the existing literature on trends in adverse birth outcomes in China specifically or globally. Many studies have approached this question examining specific exposures such as air pollution or temperature or conducted more sophisticated spatio-temporal analyses. These studies include investigations within China including a number conducted in the Guangdong province. (Liu et al BMC Public Health 2019, Liang et al Environ International 2019, etc.) The authors need to provide a better justification for why a descriptive study is needed at this time, given the existing literature and the limited analysis performed in the study. Some specific comments: 1. In the title, I would suggest using adverse birth outcomes as opposed to pregnancy outcomes as they are only looking at outcomes among live births and no investigation of outcomes in the mother. 2. The authors fail to discuss and cite the number of studies that have examined adverse birth outcomes within the Guangdong province previously. Similarly, the authors need to provide a stronger rationale for why their study is needed. How will it add to the literature above and beyond what others have already done? For example, is it more recent data, a more sophisticated spatial analysis, etc. 3. In order for readers to understand some of the spatial relationships, it would be helpful the characteristics of the Pearl River Delta and the Non-Pearl River Delta were presented to the readers. The authors briefly state there are differences in economic development, but a quantitative comparison of socioeconomic indicators would provide greater context of these areas. 4. Page 6. What is considered a "permanent birth defect"? What proportion of births meet this definition? Why was this also not analyzed as an adverse birth outcome within the study? 5. The authors mention spatial cluster detection on page 7, but no further details are provided. Was this performed and if so what methods were employed? 6. Can the authors provide additional details regarding the calculation of small for gestational age? The authors provide a

| | reference but it would be helpful for the reader if the authors briefly mentioned if this is a birthweight distribution for all of China, just the region within the study, in what time period, etc.

7. The authors make a number of recommendations regarding the need for research and interventions among poorer regions, citing differences in adverse outcomes between the different regions. Again, having quantitative evidence of the socioeconomic differences in the regions are needed to support these suggestions. |
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VERSION 1 – AUTHOR RESPONSE

To reviewer #1:
Dear Professor Oyelola Adegboye, thank you very much for these constructive comments, which have greatly improved our manuscript. Our responses to the comments are listed one by one as follows. Please check them.
1) Comment: "This is a well written and well detailed manuscript. The article presents descriptive findings using a large births data in Guangdong province of China. However, I have three major comments regarding the general introduction and statistical techniques used."
Response: Dear Professor, we really thank you for your encouragement and important suggestions. We have carefully revised the manuscript according to your comments. Thank you.

2) Comment: "The introduction lacks relevant literature on PTB, LBW and SGA situation in the study region or even China in general. It will be good to know the current incidence/prevalence of these birth outcomes in China."
Response: Dear Professor, we really thank you for your important suggestions. We have added relevant literature in the first paragraph, the Introduction part. Please check it.

3) Comment: "One of your objectives is to analyze regional differences of PTB, LBW and SGA between the Pearl River Delta and Non-Pearl River Delta regions. However, there is did not mention the statistical method you will use to make inference regarding this objective in the "data analysis" section. You also mentioned that "All statistical tests were 2-tailed. P-value less than 0.05 were considered to be statistically significant." There is no single result presented using a statistical inference in this study."
Response: Dear Professor, we really thank you for your important suggestions. We have added a statistical test to Table 2 to improve the validity of our results according to your comment in the following section. Please check it. We thank you very much for your understanding.

4) Comment: "In the same vein, the authors mentioned on page 7 line 24-26 that "We mapped the spatial distributions of rates for the adverse birth outcomes to investigate the spatial distributions pattern of the birth outcomes through 2014 to 2017." How did you confirm that there is spatial heterogeneity of birth outcomes?"
Response: Dear Professor, we really thank you for your important suggestions. According to your suggestion, we have performed spatial cluster analysis to detect spatial heterogeneity of the three birth outcomes. We calculated the Kulldorff's spatial scan statistic using the DCluster package within R software for purely spatial cluster detection of the adverse birth outcomes. Corresponding methodological details have been added in the last paragraph, the Data analysis section of the Materials and methods part. In addition, the updated results have been described in the 5th and 6th paragraphs, the Results part. Please check them. Thank you.

5) Comment: "Page 4 line 16: Insert space between 10th and percentile"
Response: Dear Professor, we have revised the typing error according to your comment. Please check it. Thank you very much.

6) Comment: "Page 4 line 16-17: "…weight falls below the 10th percentile by sex and gestational week of all singleton live Births". By this statement do you mean all singleton live births in a region?"
Response: Dear Professor, we thank you for your important suggestions. We really mean all singleton live births in a region. We have revised the sentence to make it more clearly introduced. Please check it. Thank you.

7) Comment: "Page 7 line 44-49: These statements do not read well and the 27% is not necessarily large if you compare it to 26% in 2014 and 25% in 2017. You may rewrite as: "There were a total of 2,917,098 births in Guangdong province during the study period, 1,553,948 (53.27%) were boys. Approximately 22% (627,146) babies were born in 2015, which is the lowest population of all births between 2014 and 2017.""
Response: Dear Professor, we really thank you for your important suggestions. We have rewritten the sentence according to your comment. Thank you very much.

8) Comment: "Page 8 line 5-41: The results do not present any statistical inference to support the differences observed or not observed. Adding a statistical test to Table 2 will improve the validity of your results and give credence to the presentation."
Response: Dear Professor, we really thank you for this important suggestion. We have added a statistical test to Table 2 to improve the validity of our results according to your comment. Please check it. We appreciate your opinion very much.

9) Comment: "Page 9: Add a spatial heterogeneity test to confirm the spatial variability of each birth outcomes."
Response: Dear Professor, we really thank you for your important suggestions. As we have responded to the above comment raised by you, we have performed spatial cluster analysis to detect spatial heterogeneity of the three birth outcomes according to your suggestion. In fact, this is a spatial heterogeneity test to confirm the spatial variability of each birth outcome. We calculated the Kulldorff's spatial scan statistic for purely spatial cluster detection of the adverse birth outcomes. Corresponding methodological details have been added in the last paragraph, the Data analysis section of the Materials and methods part. In addition, the updated results have been described in the 5th and 6th paragraphs, the Results part. Please check them. Thank you.

10) Comment: "The discussion is well written, however, it is essential that the authors discuss in depth the reasons for the differences observed between the regions and seasons."
Response: Dear Professor, we really thank you for your important suggestions. In fact, the reasons for the differences observed between the seasons have been discussed in depth in the 3rd paragraph, the Discussion part. Please check it. For the discussion of the reasons for the differences observed between the regions, we have added more content to discuss it in depth according to your suggestion. Please check them in the 4th paragraph, the Discussion part. Thank you very much.

To reviewer #2:

Dear Professor Jeanette Stingone, we really thank you for giving us this opportunity to revise the manuscript based on your constructive comments, which have greatly improved our manuscript. Our responses to the comments are listed one by one as follows. Please check them.

1) Comment: "The authors conducted a descriptive analysis examining the patterns of adverse birth outcomes in Guangdong China. It is unclear what this study adds to the existing literature on trends in adverse birth outcomes in China specifically or globally. Many studies have approached this question examining specific exposures such as air pollution or temperature or conducted more sophisticated spatio-temporal analyses. These studies include investigations within China including a number conducted in the Guangdong province. (Liu et al BMC Public Health 2019, Liang et al Environ International 2019, etc.) The authors need to provide a better justification for why a descriptive study is needed at this time, given the existing literature and the limited analysis performed in the study. Some specific comments:"

Response: Dear Professor, we thank you for your comments. In fact, your above comment is right. Some studies (Liu et al BMC Public Health 2019, Liang et al Environ International 2019, etc.) have examined specific exposures such as air pollution or temperature on adverse birth outcomes in Guangdong China. Among them, our recent study (please refer to: Pi Guo, et al. Maternal exposure to gaseous ambient air pollutants increases the risk of preterm birth in the Pearl River Delta, China 2014-2017. Sci Total Environ. 2019) based on a large population has also examined the effects of ambient air pollution on preterm birth. However, we found that there is a lack of a description of the general situation of the incidence of adverse pregnancy outcomes (PTB, SGA, and LBW) in the study site, which is the southern gate of China and has the most developed economic and social level in South China at present. We believe that there is an urgent need to provide an overall description of the fertility situation of the local population in order to carry out the follow-up exploratory study. We think the findings will contribute to the understanding of the etiology and epidemiology of PTB, LBW and SGA, and the design of prevention and intervention strategies for specific geographical areas and high-risk populations. Therefore, we performed the present research to fill this gap. According to your comment, we have further described the justification for why a descriptive study is needed at this time. Please check it in the 3rd paragraph, the Introduction part. We really appreciate your understanding.

2) Comment: "In the title, I would suggest using adverse birth outcomes as opposed to pregnancy outcomes as they are only looking at outcomes among live births and no investigation of outcomes in the mother."

Response: Dear Professor, we really thank you for your important comments. The title has been revised according to your suggestion. Please check it.

3) Comment: "The authors fail to discuss and cite the number of studies that have examined adverse birth outcomes within the Guangdong province previously. Similarly, the authors need to provide a stronger rationale for why their study is needed. How will it add to the literature above and beyond what others have already done? For example, is it more recent data, a more sophisticated spatial analysis, etc."

Response: Dear Professor, we really thank you for your important comments. First, we actually have cited relevant studies that have examined adverse birth outcomes within the Guangdong province as well as in other regions of China. Please check them in the 3rd and 4th paragraphs, the Discussion part. In order to discuss in depth the content, we have also cited more relevant studies in the 4th paragraph, the Discussion part. Second, we have accepted your suggestion that "the authors need to provide a stronger rationale for why their study is needed". Actually, we have introduced relevant content in the 2nd paragraph, the Introduction part. In addition, according to your comment, we have further described the justification in the 3rd paragraph, the Introduction part. Third, for your comment "How will it add to the literature above and beyond what others have already done", we have

discussed the contribution of our research in the 1st paragraph, the Introduction part, according to your suggestion. Please check it. We really appreciate your understanding.

4) Comment: "In order for readers to understand some of the spatial relationships, it would be helpful the characteristics of the Pearl River Delta and the Non-Pearl River Delta were presented to the readers. The authors briefly state there are differences in economic development, but a quantitative comparison of socioeconomic indicators would provide greater context of these areas."
Response: Dear Professor, we thank you for your comments and encouragement. In fact, it is difficult for us to obtain the overall information of the socioeconomic indicators of the two areas (actually the two areas contain more than 20 cities) corresponding to the study time period at this present study. We really thank you for your suggestion, and we think this important issue should be explored in our future work. In fact, in order to provide a quantitative comparison of adverse birth outcomes of the Pearl River Delta and the Non-Pearl River Delta, we have performed a statistical test, and the analysis results have been added to Table 2 to improve the validity of our results according to your comment. Please check it.

5) Comment: "Page 6. What is considered a "permanent birth defect"? What proportion of births meet this definition? Why was this also not analyzed as an adverse birth outcome within the study? "
Response: Dear Professor, thank you very much. In fact, the "permanent birth defect" is a typing error. It should be "birth defect". We have revised the error. Please check it. For the comment "why was this also not analyzed as an adverse birth outcome within the study", we thank you for giving us this opportunity to explain to you here. Our present study only focused on three main adverse birth outcomes including PTB, SGA and LBW of local residents. Certainly, the "birth defect" is one of the adverse birth outcomes. However, in order to fully depict the situation, we think a study we are now doing is a detailed analysis of the birth defects in Guangdong province. Because the outcome of birth defects involves extraordinary events, it needs to be presented with a complete study. We thank you very much for your understanding.

6) Comment: "The authors mention spatial cluster detection on page 7, but no further details are provided. Was this performed and if so what methods were employed? "
Response: Response: Dear Professor, we really thank you for your important suggestions. According to your suggestions, we have performed spatial cluster analysis to detect spatial heterogeneity of birth outcomes. This is a spatial heterogeneity test to confirm the spatial variability of each birth outcome. We calculated the Kulldorff's spatial scan statistic for purely spatial cluster detection of the adverse birth outcomes. Corresponding methodological details have been added in the last paragraph, the Data analysis section of the Materials and methods part. In addition, the updated results have been described in the 5th and 6th paragraphs, the Results part. Please check them. Thank you.

7) Comment: "Can the authors provide additional details regarding the calculation of small for gestational age? The authors provide a reference but it would be helpful for the reader if the authors briefly mentioned if this is a birth weight distribution for all of China, just the region within the study, in what time period, etc."
Response: Dear Professor, we really thank you for your professional comments. In fact, this issue has been also pointed out by Reviewer #1 and we have modified the description to make its expression more accurate and clear. Please check it.

8) Comment: "The authors make a number of recommendations regarding the need for research and interventions among poorer regions, citing differences in adverse outcomes between the different regions. Again, having quantitative evidence of the socioeconomic differences in the regions is needed to support these suggestions."
Response: Dear Professor, we really thank you for your important comments. For this comment, we've explained this issue to you in the above section. Please check them in the above comments #3

and #4. In fact, in this present study we don't have access to comprehensive information of the socioeconomic indicators of the two areas (actually the two areas contain more than 20 cities). We really thank you for the understanding, and would like to investigate this issue in our future work. Thank you again.

VERSION 2 – REVIEW

REVIEWER	Oyelola Adegboye, PhD James Cook University, Australia
REVIEW RETURNED	18-Sep-2019

GENERAL COMMENTS	This is a much improved version of the original manuscript. The authors have tackled the comments in my first review. Please see my comments below for minor revision. Page 5 line 17-19. Provide reference for this statement Page 7 line 7-12: The sentence seems incomplete. Are you saying? We described basic characteristics of the newborns and mothers, and the rates of PTB, LBW and SGA according to the studied characteristics by year and compered the estimates using χ2 test? Page 11 line 19. The authors wrote "As we known, there are obvious regional differences in the social and economic level, diet structure and educational level in Guangdong province." They assumed the readers know the regional difference in Guangdong province. Please rephrase and add a reference to it.

VERSION 2 – AUTHOR RESPONSE

To reviewer #1:

Dear Professor Oyelola Adegboye, thank you very much for these constructive comments, which have greatly improved our manuscript. Our responses to the comments are listed one by one as follows. Please check them.

1) Comment: "This is a much improved version of the original manuscript. The authors have tackled the comments in my first review. Please see my comments below for minor revision."

Response: Dear Professor, we really thank you for your encouragement and giving us this opportunity to revise the manuscript. We have carefully revised the manuscript according to your comments. Thank you.

2) Comment: "Page 5 line 17-19: Provide reference for this statement."

Response: Dear Professor, thank you very much for the insightful comments. According to your suggestion, we have added a reference for this statement. Please check it. Thank you very much.

3) Comment: "Page 7 line 7-12: The sentence seems incomplete. Are you saying?

We described basic characteristics of the newborns and mothers, and the rates of PTB, LBW and SGA according to the studied characteristics by year and compared the estimates using χ2 test? "

Response: Dear Professor, thank you very much for the insightful comments. We have revised the sentence according to your suggestion. Please check it.

4) Comment: "Page 11 line 19: The authors wrote "As we known, there are obvious regional differences in the social and economic level, diet structure and educational level in Guangdong province." They assumed the readers know the regional difference in Guangdong province. Please rephrase and add a reference to it."

Response: Dear Professor, thank you very much for the insightful comments. We have rephrased the sentence and add a reference to it according to your suggestion. Please check it.