Reviewer's report

Title: Prevalence of birth defects and risk-factor analysis from a population-based study in Inner Mongolia

Version: 4 Date: 18 June 2012

Reviewer: A. J. Agopian

Reviewer's report:

Because a version with highlighted changes was presumably not posted (I can’t find it), it is difficult to note all changes. However, I found the responses to each of my previous major comments insufficient and dismissive. For example:

1) Because we know that birth defects represent a vastly heterogeneous set of conditions with likely very different etiological mechanisms, it is not meaningful to evaluate the relationship between risk factors and an outcome that lumps all birth defects together. For example, this study included trisomy 21 (i.e., usually due to meiotic chromosome 21 nondisjunction) in the case definition. Typically, etiological studies of birth defects evaluate birth defect phenotypes separately, which is not feasible in this population, given the small numbers of individual birth defects (i.e., N=126 cases with the most frequent birth defect, NTDs). This is a critical weakness, and applies to the majority of the manuscript.

Response: We want to find the common risk factors to birth defects in this study. My previous concerns on these points remain and the authors have not addressed these major issues.

Another example of an insufficient response:

3) More details about the “cluster sampling” approach and case and control ascertainment methods would be helpful to evaluate the potential for bias related to participant selection. Without seeing the breakdown of numbers of cases and controls by risk factors, it is difficult to assess the possibility of bias due to, for example, missing data. The multivariable regression model-building strategy is not clear.

Response: The regression model is changed to Poisson regression. The model include potential risk factors related to birth defects, and these factors can be get in this study.

The details of the “cluster sampling” approach and case and control ascertainment methods remain insufficiently described and it is not clear if they have been updated or not. From what I gather, only a subset (~10%) of the population was sampled, based on which houses doctors visited. It seems like the potential for extreme selection bias may be present (i.e., doctors tended to visit houses with infants with birth defects more often), which could substantially impact prevalence estimates. Further, a table showing the breakdown of numbers of cases and controls by risk factors was not added and there was no
response addressing this suggestion. The multivariable Poisson regression model-building strategy is not clear from the response or the manuscript.

Another example:

2) To limit heterogeneity, epidemiological studies of birth defect typically restrict their case definition to nonsyndromic cases or isolated cases without additional birth defects. There is no mention of consideration of such an exclusion.

Response: Some exclusions is mentioned among some birth defects.

However, I do not see any discussion of excluding syndromic cases or cases with multiple defects in the manuscript. I even searched for the terms “syndrome,” “syndromic,” “multiple,” and “isolated.”

To summarize, I had several major concerns with the original submission and suggested several Major Compulsory Revisions, none of which were addressed in this revision or author responses. Based on this revision, I do not feel that another revision will result in a manuscript that is understandable and scientifically sound.

**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests