Author’s response to reviews

Title: Association of Maternal Ethnicity and Urbanicity on Severe Pediatric Disease: A Nationwide Cohort Study

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Version: 1 Date: 18 Nov 2019

Author’s response to reviews:

Dear editor and reviewers:

We thank for the helpful and generous comments to improve our paper. We have addressed all the comments point by point. The texts and table revised were marked in red and underlying for easy reading. We hope that our paper is now acceptable for publication.

Reviewer reports:
I-Min Chiu (Reviewer 1): Thank you for your hard work on this manuscript. The authors describe a nationwide cohort study based on National Health Insurance Research Database registry during 2004-2015. This is a very interesting topics since Taiwan has gradually become a multiracial society in past few decades. The design and analysis of this study is well performed. I only have few questions regarding the data collection in this articles.
1. line 1, page 6. You mentioned that differentiation of urban and rural population was defined by based on 7 urbanization levels for the 359 townships of Taiwan, proposed by Liu et al. Were this classification based on children's birthplace or their hospital visit area? Since this is a cohort study follow up over 10 years, how is a child be classified if he/she moved from urban to rural area or conversely during study period?
Ans: The classification of urban or rural was based on household registration of the mothers when they gave birth of the study children in this study. In other words, the status of urban or rural would not be changed over the 10 years of follow-up. We realized that some child may move from urban to rural area or vise versa but such proportion is very small. We added the explanation in the covariate section (please see p.6, line 6-8 this submission) and included this as our limitation. (Please see p.14, line 9-14...
this submission)

2. line 7, page 12. "In addition, better accessibility of level II prenatal sonography in urban areas and selective termination of pregnancies in which the fetus exhibits major congenital circulatory anomalies before gestational age 24 weeks might partly explain the lower incidences of these conditions in urban areas." I'm not sure about this explanation. Did you mean compared to rural area, urban area mother has better accessibility of high level prenatal exam and they tend to terminate pregnancy in major fetus anomalies condition?

Ans: Yes. We presumed that better prenatal screen may contribute to higher termination rate with major fetal anomalies, no matter what ethnicity the mother is. Unfortunately, the annual termination rate in Taiwan is unavailable as the notification of artificial abortion before 24 weeks of gestation to the health authority is not mandatory. Therefore, we were unable to show the difference in termination rate between urban and rural areas. In addition, the law in Taiwan allows abortion for reasons of fetal, maternal, or social factors, if it is performed prior to 24 gestational weeks. The better accessibility of self-paid high level antepartum screen might “partly” explain the findings we observed. Please see p.12, line 20-22 and p.12, line 25 to p.13, line 1-3, this submission.

3. line 12, page 13. As you mentioned in limitation part, the incidence of selected disease in this study were quite different compare to epidemiological data. This may have much bigger effect on FBM/TBM and result in diminished healthy migrant effect.

Ans: Yes, we added “We anticipated that bigger effect of FBM/TBM or urban/rural on children’s mild health outcome.“ in the limitation (Please see p. 14, line 3-4 this submission).

Ming Chih Lin (Reviewer 2): This is a paper analyzing clam data from the national health insurance of Taiwan. I have several comments here.

1. The authors did not describe how ethnicity was defined from the data base. It should be described in detail because selection bias may exist by misclassification of exposure.

Ans: TBMs or FBMs was based on the maternal nationality from TBR. TBMs were the mothers whose nationality were Taiwan; whereas FBMs were the mothers whose nationality were foreign countries. Please see p.6, line 4-6, this submission. We also added the percentage of nationality of FBMs in the result. “Regarding to nationality of FBMs, mainland China (52.94%) was the predominant country, followed by Vietnam (33.01%), Indonesia (7.29%), Philippines (2.24%), Thailand (1.94%), Cambodia (1.31%), Myanmar (1.28%) “. Please see p.7, line 24 to p8, line 1-2, this submission.

2. Urban and rural areas definition was not described at all. This point should also be described in detail because the major conclusion of this article discussion about it.

Ans: We added the detail information of urban and rural areas as “the classification of urban or rural was based on the township in household registration of the mothers when they gave birth of the study children. In Liu’s study, they included population density (people/km2), population ratio of people with college or above educational levels, population ratio of elder people over 65 years old, population ratio of people of agriculture workers and the number of physicians per 100,000 people and used the cluster analysis with squared Euclidean distance and Wald’s minimum variance method, to study the urbanization stratification of varied township in Taiwan. They identified 7 clusters for the 359 townships of Taiwan: highly urbanized town, moderate urbanization town, emerging town, general township, aging town, agricultural town, remote towns and villages“. [Liu CY, Hung YT, Chuang YL. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. J Health Management (Chin) 2006; 4: 1–22] (Please see p.6, line 6-16, this submission) We did a google scholar search on Nov. 14, 2019 and there were 509 citations on Liu’s article. We are confident that the creditability of Liu’s study.
3. The outcomes were from catastrophic disease certificate. I don't think this is a reliable outcome measurement. The authors should describe the validation of outcome measurement in the methodology section.
Ans: As all electronic health databases, much concerns have been addressed about the validity. To avoid up-coding or misclassification of pediatric severe diseases, we analyzed patients with the catastrophic disease certificate (CRC). In Taiwan, registration of catastrophic disease certificate (CRC) as a catastrophic illness is approved after evaluating clinical evidence and a comprehensive review by Taiwan National Health Insurance Administration to determine eligibility for exemption from all co-payments. For instance, pathologic and/or cytologic reports are required for oncologists to get the CRC for cancer patients. A study that used the Taiwan Cancer Registry to validate cancer diagnoses in the NHIRD reported a high positive predictive value (94%) [Kao WH, Hong JH, See LC, et al. Validity of cancer diagnosis in the National Health Insurance database compared with the linked National Cancer Registry in Taiwan. Pharmacoepidemiol Drug Saf 2018;27:1060–1066.] Other studies on heart failure, neurologic disorders showed similar results [Hsieh CY, Su CC, Shao SC, et al. Taiwan’s National Health Insurance Research Database: past and future. Clinical Epidemiology 2019:11 349–358].

4. For the analysis, I did not see any covariate adjustment in the tables and figures. I think the authors should describe those possible confounding factors in detail.
Ans: We did adjust for the grouping of birthweight-gestational-age, sex, and maternal age, because we studied numerous health outcomes (please see the explanation of the covariate but not in the statistical analysis, p. 6, line 7-8 in the previous submission). We removed the above sentence from the section of covariate and revised the statistical analysis as “Other than the status of the study group, we also included the grouping of birthweight-gestational-age, sex, and maternal age in the Cox proportional hazard model, because we studied numerous health outcomes.” (Please see p. 7, line 6-9 this submission) We also added a statement “The hazard ratio was adjusted for the grouping of birthweight-gestational-age, sex, and maternal age using the Cox proportional hazard model.” in the figure title of Figure 3. (Please see p. 20, line 10 this submission).