Author’s response to reviews

Title: Maternal iodine status during lactation and infant weight and length in Henan Province, China

Authors:

Jin Yang (yangjin6429@163.com)
Lin Zhu (zhulin_pro@163.com)
Xiaofeng Li (lixf_99@hncdc.com.cn)
Heming Zheng (zhming99@sina.com)
Zhe Wang (wangz@hncdc.com.cn)
Zongyu Hao (haozy@hncdc.com.cn)
Yang Liu (Liuy@hncdc.com.cn)

Version: 1 Date: 21 Apr 2016

Author’s response to reviews:

Reviewer #1: This is a cross-sectional study examining the relation between maternal and infant iodine status in a province in China with infants' anthropometric measures. The analyses showed that the population under study was iodine sufficient. However, in 747 mother-child pairs (who had exclusive breastfeeding in the first 6 months of infant's life) the authors showed that maternal urinary iodine concentration (UIC) <50 μg/L was associated with smaller anthropocentric indices. This is an area of research that needs further attention since few studies focus on the iodine status of lactating women and its importance for child health.

My comments:

Title: the study uses one single time point of anthropometric measures. So the use of the term "infant growth" can be misleading, because "growth" implies that longitudinal data of anthropometric measures were available in the study.

The authors’ answer:

Thanks for your suggestion. The term "infant growth" in the title has been corrected as "infant weight and length".
Abstract: Please indicate the study design (cross-sectional study). Also define the abbreviation used. It would be informative if the number of women and infants with UIC<50 μg/L is also listed. I suggest that the conclusion would be rephrased as the study did not actually measure "growth".

The authors’ answer:
We are so sorry for our negligence in the abstract. The sentence "A cross-sectional survey of maternal iodine status and infant anthropometric measures was conducted" has been added into the abstract. All the abbreviation used were given the full name, such as "weight-for-age Z-score (WAZ), height-for-age Z-score (HAZ) and body mass index (BMI) by the World Health Organization (WHO)". The number of women and infants with UIC<50 μg/L was listed, which were 41 and 20 respectively. The conclusion has been revised as "Our study suggests that maternal iodine status may be related to their infant anthropometric index. Appropriate iodine intake of lactating women is beneficial for their infants."

Introduction: Lines 75-78 discuss the limitation of previous studies, and provide the rationale for the present study. Please be more specific about each of the point brought up by using examples, e.g. what was the sample of the previous studies (small), or what was the potential confounder which was missed in the previous studies. Also, it would be worth mentioning if any trial has addressed the benefit of iodine supplementation in lactating women (and can be extensively reviewed in the discussion too).

The authors’ answer:
The examples have been cited in the Line 78-81. "For example, an Argentina study was restricted by a small sample size (n=77) [19]. Another study from Bangladeshi was based on a micronutrient supplementation trial (n=1617) without considering the genetic effect [20]".

There are few studies about the benefit of iodine supplementation in lactating women. Some references have been cited in the discussion, Line 209-213 "An iodine supplementation trial from Bangkok [37] reported that BMIC and infant UIC in supplemented group were higher than the values in non-supplemented group, and cord serum TSH of infant had a decline after iodine supplementation. Morse [38] proved that maternal supplementation of vitamin D, DHA, folic acid and iodine during pregnancy and lactation can be beneficial for brain development of their offspring."
Methods: UIC measures were not adjusted for the creatinine clearance. It should be mentioned as an important limitation of the study. Also, what was the rationale for adjustment for maternal iodine supplementation? Does it have a direct effect on infant anthropometric measures independent of maternal or child UIC? Another question is, why in the regression models, maternal and infant UIC were entered simultaneously?

One suggestion would be to examine the effect of maternal UIC in the group of children who had UIC within the normal range (excluding high infant UIC or infants with UIC <50 μg/l. If any association will be observed between maternal UIC and child anthropometric measures in this group, it will be an indication for the direct effect of maternal UIC on infant anthropometric measures.

The authors’ answer:

We are very sorry for not measuring urine creatinine. The ratio of urinary iodine and creatinine can reflect the real iodine intake of individuals by excluding the influence of urinary concentration and dilution. The method has ever been used for our surveillance in China. However, considering the complexity of the method and the difficulty of obtaining different normal values in different populations, determine iodine in urine by the acid digestion method (WS/T107-2006) are recommended as a national standard method developed by the China’s Ministry of Health. The limitation has been discussed in Line 248-250.

The variable of “maternal iodine supplementation” was deleted from the multiple regression, since it has been reflected by maternal UIC.

We completely agree with this valuable suggestion by the reviewer. It was inappropriate that maternal and infant UIC were entered simultaneously in the regression models as there is collinearity among them. According to the suggestion, only women whose children had UIC within the normal range (50-299μg/L) were included (n=451) in the multiple regression. The corresponding part has been adjusted.

Results: Line 145, additional to the group level measures, please provide what percentage had UIC within the range recommended by WHO.

The authors’ answer:

According to the WHO criterion, a median UIC 100μg/L or higher define both mother and infant as iodine sufficient. So, the sentence "the percentages of the mothers and their infants with UIC above 100 μg/L were 81.0% and 92.7%, respectively" has been supplemented.
Discussion: an important issue for recommendations on iodine intake is the safe range. A growing body of literature suggests the impact of low levels of iodine as well as high levels in pregnant and lactating women on child health. The authors are suggested to target this issue in their analyses and also comment on it in the discussion. Also, the lack of evidence in lactating women should be discussed further and the existing interventional studies with iodine supplementation in lactating women can be reviewed.

The authors’ answer:

We appreciate the reviewer to propose the point. In our study, the highest HAZ, WAZ was in the infants whose mothers had UIC between 50 and 99 μg/L. The highest BMI was in the infants whose mothers had UIC between 200 and 299 μg/L. The highest values were in the middle UIC group, not the highest UIC group. But in our result, the impact of iodine deficiency on infant anthropometric index outweighs the impact of iodine excess. In order to describe more clearly, the according part in the abstract, result and discuss has been revised. The discussion about lactating women has been stated further in Line 228-233. The existing interventional studies with iodine supplementation in lactating women have been reviewed in Line 209-213 and Line 239-242.

Line 205, I am not sure if this recommendation is in line with the findings. Despite the fact that UIC at the group level was within the WHO recommendation, there was a percentage of women who had UIC below the recommended levels and the children of these women had smaller anthropometric measures compared to the rest.

The authors’ answer:

This recommendation in Line 205 has been deleted as it seems to be improper.

Reviewer #2: 1. Abstract:

1. Aim of study: '… evaluate impact of maternal and infant iodine… infant growth' is not correct as it implies cause-effect, which was not the case. Suggest to change to '… association between maternal and infant UIC and…'

The authors’ answer:

The word ‘impact’ has been replaced with the word ‘association’ in the aim.
2. Conclusion - the results were not conclusive on the relationship between maternal UIC and infant growth.

The authors’ answer:

The conclusion has been modified as ‘Our study suggests that maternal iodine status may be related to their infant anthropometric index. Appropriate iodine intake of lactating women is beneficial for their infants.’

2. Methods:

a. Subject: First paragraph: explanation of the sample is not consistent with the presented results. It was mentioned that ‘A total of 1598 infant-mother pairs were enrolled …. and included in the analysis about relationship between infant iodine and growth.’ The following sentence indicated that only exclusive breastfeeding (EBF) mothers and their infants <6 mo (n=747)….for correlation analysis. Therefore, it is better to make it clear if this paper will present analysis of data from EBF mother-infant pairs and accordingly, all tables focus on this group.

The authors’ answer:

Thanks for your suggestion. All the parts about 1598 infants were deleted. This paper was revised to only analyze the exclusive breastfeeding (EBF) mothers and their infants <6 mo (n=747).

b. Statistical analysis: it is indicated that Pearson's correlation was used. This gives the answer on whether the two variables relate, but observing the data presentation in Table 2, using kappa statistic will give additional data on the concordance/ discordant of the UIC between mother's and infant's UIC.

The authors’ answer:

Actually, two ordinal variable relations are fit for consistence check and Kappa test. I am afraid that Kappa test is more suitable for the same samples. In our study, infant UIC were significant higher than their mothers (177.4 vs 261.1 μg/L). One reason is that the lactating women would transfer part of iodine into breast milk. Another reason is that infant thyroid and renal functions are not immature and excess iodine can not be storied. So, breast-fed infant UIC is significantly related to their mothers, but they lack of good consistence (kappa value=0.07).
3. Results:

a. Second paragraph under the 'Characteristics of mothers and infants': these data are for all children (n=1658). What is the purpose for presenting these data? What do they add to the understanding of the finding?

The authors’ answer:

We are so sorry to mistake the number, and it should be 1598. In the original paper, we analyze 1598 infant data for infant iodine status and their anthropometric measures. This part is to depict the characteristics of 1598 infants as table 1 only provide the basic information of 747 infant-mother pairs. In the present paper, only exclusive breastfeeding (EBF) mothers and their infants <6 mo (n=747) were analyzed. So the paragraph became unnecessary and was deleted.

b. Relationship between maternal and infant UIC (lines 148-151: see suggestion in 2(b)

The authors’ answer:

The consistence check has been done and the kappa value has been presented in the part.

c. Relationship between maternal UIC and infant growth (Lines 152-157): Please check the last two sentence which one (HAZ and WAZ) was statistical significant.

The authors’ answer:

WAZ was statistical significant and the last two sentence was corrected.

d. Line 163: ' .... significantly lower than those with maternal UIC ....' And refer to Table 4. Is it infant UIC which was analysed with infant growth?

The authors’ answer:

In table 4, it shows the correlation between infant UIC and infant anthropometric measures. Is ‘significantly lower than those with maternal UIC’ refers to the sentence ‘Analysed by t test, the infant HAZ with maternal UIC below 50μg/L were significantly lower than those with maternal UIC of 50μg/L or more (p=0.043)’? It compares the mean anthropometric indexes between maternal UIC <50 and 50 or higher after maternal UIC has been reclassified into 2 groups, instead of 5 groups.
e. Lines 174-178: from Table 5, is it infant UIC (not maternal) <50 µg/L … significantly lower BMI…."?

The authors’ answer:

We are so sorry for the mistake. It is infant UIC, not maternal UIC in line 174-178. According to another reviewer’s comment, only infants who had UIC within the normal range (excluding high infant UIC or infants with UIC <50 µg/l were included to reflect the direct the direct effect of maternal UIC on infant anthropometric measures. So, the part about infant UIC has been deleted in the revised paper.

f. Table 1: footnote a there is no indication where is a in the table.

The authors’ answer:

Footnote a has been deleted since we did not analyze 1598 infants.

g. Table 3: please add appropriate statistical test.

The authors’ answer:

In table 3, ANOVA was used to compare mean anthropometric indexes between 5 different UIC groups. But the lowest values are in the maternal UIC group <50 µg/L, and other four group has small difference. So, there was no significant difference between 5 different UIC groups. We reclassify UIC group into two groups as maternal UIC <50 and 50 or higher. T-test has been reanalyzed the difference of two groups. The difference between maternal UIC <50 and 50 or higher was significant.

h. Table 4: Title, there is no maternal UIC in this Table.

The authors’ answer:

Maternal UIC in the title of Table 4 has been deleted.

i. Table 5: What does this multiple regression address (infant's nutritional status (HAZ, WAZ, BMI) and what, while adjusted for possible confounding variables)? It is not meaningful to just analyze using multiple regression without having a specific question to be answered. Title should be modified accordingly.
The authors' answer:

The title in table 5 has been modified as ‘Adjusted association between maternal UIC and infant HAZ, WAZ, and BMI, using multiple linear regression’.

4. Discussion:
   
a. Second paragraph: Lines 188-195: it is not clear what is the conclusion based on the current study and that in the literature - infant UIC and BMIC (pls put full words) but not maternal UIC and infant UIC?

The authors’ answer:

BMIC was modified as Breast-milk iodine concentration. Infant UIC may have a stronger correlation with BMIC than maternal UIC. Due to the limitation of experimental condition and easily accessibility, maternal UIC were used to replace breast-milk iodine concentration (BMIC). In the paragraph, two reference about the relationship between maternal UIC and infant UIC replaced with the old reference about infant UIC and BMIC. The corresponding modification was presented in Line 195-198.


5. Other comments:
   
a. Line 201 - please use full name of the country, Switzerland.

The authors’ answer:

The country were given the full name ‘Switzerland’.

b. Please check typo errors
We carefully proof read the manuscript to correct the typographical, grammatical, and bibliographical errors,

c. Some English editing is needed.

The manuscript was edited by the help of someone skilled and familiar with scientific English.

Editorial Comments:

STROBE guidelines

In accordance with BioMed Central editorial policies (http://www.biomedcentral.com/submissions/editorial-policies#standards+of+reporting), could you please ensure your manuscript reporting adheres to STROBE guidelines (http://www.strobe-statement.org/) for reporting observational research. This is so your methodology can be fully evaluated and utilized. Can you please include a completed STROBE checklist as an additional file when submitting your revised manuscript.

The authors’ answer:

According to STROBE guidelines, we completed a STROBE checklist as an additional file.

We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service. Please see the following for further details: http://bmcpregnancychildbirth.biomedcentral.com/submission-guidelines/preparing-your-manuscript#preparing+main+manuscript+text

The authors’ answer:

The final manuscript was edited by the help of Dr. Chun-yu Liu (Framingham Heart Study in the United States) to improve the style of written English.

Please ensure all main section headings are as outlined in the journal author instructions, including the declarations sections at the end of the manuscript. Please also add a Conclusions heading.

Please add (after the conclusions) a list of abbreviations used.

The authors' answer:
We carefully check all main section headings which are generalized the main details of the journal.

A Conclusions heading was added at the end of the manuscript.

A list of abbreviations used was added after the conclusions as a single part.