Author’s response to reviews

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

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Author’s response to reviews:

Reviewer #1: The authors addressed the comments and the manuscript has approved considerably. I have a few minor comments.

1. The authors are strongly suggested to review the manuscript for the inappropriate use of "growth" and "impact" and to consider replacing them with "anthropometric measures" and "association". A few examples are: page 5, two sub-headings, on line 180 and 190; or page 8, line 284.

The authors’ answer:

Thanks for your suggestion. The words "growth" and "impact" are replaced with "anthropometric measures” and "association"(e.g. Result section, line149, 163, page 5; Discussion section, line 216, page 6).

2. Please refer to the cross-sectional design of the study in the limitation section, and that no inference regarding the causality of this association or the "impact" of maternal iodine levels in lactating women can be made.

The authors’ answer:
We completely agree with this valuable suggestion by the reviewer. The inappropriate word “impact” has been deleted or replaced. (e.g. Background section, line76, page 3)

3. Please delete "its impact on" from the title as it may suggest a causal association.

The authors’ answer:

The word "its impact on" has been deleted from the title.

4. In the introduction, reference 20 and the comparison made are irrelevant and also the limitation mentioned (not considering for genetic factors) is not related to a trial. Please consider removing it.

The authors’ answer:

Thanks for your suggestion. Reference 20 and the corresponding sentence in the background have been deleted. (e.g. Background section, line75, page 3)

Reviewer #2: Thank you very much for your thorough responses to reviewer's comments. However, there are issues from the subject matter point of view that is essential to be improved.

1. Use of anthropometry for assessing 'nutritional status' of infants and young children. Three common indicators are used, namely, weight-for-age z-score (WAZ, underweight), height-for-age z-score (HAZ, stunting) and weight-for-height z-score (WHZ, wasting), according to WHO. It is not appropriate to use BMI since children still have growth. WHO has recommended also the use of BMI z-score, but often used for older children.

The authors’ answer:

Thanks for your suggestion. All the calculation or results related to infant BMI have been deleted, including table 3-4.

2. UIC from casual urine is NOT a measure of 'iodine status'. Its median however is a measure of population-level of iodine sufficiency.

The authors’ answer:
WHO recommended UIC as the most practical biomarker for assessing iodine nutrition in a population (WHO, Assessment of the iodine deficiency disorders and monitoring their elimination, 2 edn, 2001), although not in individuals since it reflects recent iodine intake. However, low UIC probably reflect a prolonged low iodine status in an individual (Soldin OP, et al, Therapeutic drug monitoring, 2005, 27 178-185). In our study, a categorization in five UIC groups instead of using the continuous variable diminished the possible misclassification bias, due to daily variations of iodine intake.

3. There is evidence that BMIC correlates with UIC, hence this supports the use of UIC in this study as a proxy of BMIC, and should be stated. This may be included in the discussion. A few references that may be useful below.


4. Specific comments on Results:

a. Table 2, please include statistical test underneath the Table (r & p-value)

The authors’ answer:
Statistical test was added on the bottom of table 2, e.g. maternal UIC was positively correlated with infant UIC (r=0.203, P<0.001).

b. Text reference to Table 3: 'In the maternal UIC group'. From the presented data, I understand that authors refer to the association between 'maternal UIC and infant nutritional status' (no 'group'). Similarly, that for 'infant UIC group' (text for Table 4) should be 'infant UIC'.

The authors’ answer:
Thanks for your suggestion. Maternal UIC group are revised as maternal UIC. (e.g. Result section, line 150, page 5). The result about Infant UIC and infant size and Table 4 has been deleted, because no significant difference was found.

c. Based on the UIC data of both lactating mothers and infants, this population seems to be 'iodine sufficient'. In addition, the anthropometric data based on mean HAZ and WAZ do not
seem to be an undernourished population. Therefore, it is not surprising for not seeing any association between UIC and respective anthropometric indicators. Nevertheless, if the authors still want to present these data (Table 3 & 4), please put the statistical test underneath the Tables, although they are NS.

The authors’ answer:

The statistical test results (P value) have been added underneath Table 3. Table 4 has been deleted, because no significant difference was found between Infant UIC and infant size.

d. Is there any data on the household % coverage of iodized salt from the studied sample? If there is, it should be included. If not, but there is coverage data for this area, it may be mentioned in the discussion.

The authors’ answer:

China began to adopt the policy of universal salt iodization in 1995. Salt iodine concentration in the households is a routine national surveillance. In each year, 300 salt samples of the households are selected from each county. Based on the national survey in 2014, the household coverage rates with iodized salt was 93.3% in Henan province. (e.g. Discussion section, line 169-170, page 5).

e. Multiple regression (text and Table 5): It is not clear whether the authors addressed the question, 'Is there any relationship between maternal UIC and child nutritional status (anthropometry). If so, the inclusion of factors other than maternal UIC are for controlling for potential confounders, and hence, only the beta-coefficients of the factors be presented. The coefficients of subcategories of each confounder are not meaningful for the interpretation of the main effect (maternal UIC). Why included 'paternal weight' as a confounder? If the reasons being parental status may affect child's status, then maternal BMI and maternal & paternal height may be appropriate (if data are available). Please consult your statistician.

The authors’ answer:

Thanks for your suggestion. The coefficients of subcategories of each confounder are excluded from Table 5. Only the coefficients of maternal UIC are kept. Maternal height and weight, paternal height and weight are all available. In our previous analyze, maternal height and paternal height were included in the regression model of HAZ (infant height score), maternal weight and paternal weight were included in the regression model of WAZ (infant weight score). Based on previous model, only paternal weight was significant related to their infant weight, so it was kept in table 5. According to your suggestion, we adjusted maternal and paternal height in the new regression model of HAZ, and only adjusted maternal BMI in the new regression of WAZ.
f. Editorial note for Table 5: since the confounding factors adjusted in all models (HAZ, WZ, BMI) as presented in the footnotes below the table are the same. Hence, the variables included in the adjusted model can be indicated only once, rather than a lengthy repetitive mention. Also, remove the footnote, 'eOnly significant variables were presented' since this is not relevant in the context of analysis here.

The authors’ answer:

The confounding factors in model HAZ were not consistent with the factors in model WAZ. In HAZ model, maternal and paternal height, and other confounding factors (maternal income, occupation, et al) were adjusted. However, only maternal BMI and other confounding factors (maternal income, occupation, et al) were adjusted in WAZ model, not including maternal and paternal height. So the confounding factors of the two models were presented in the footnotes, respectively. The sentence 'Only significant variables were presented' has been deleted from the footnote of table 5.

5. Discussion:

a. Based on the UIC median and IQR of both lactating mothers and infants appear to be in the relatively 'normal range', the basis for analysis of either the low or high end of UIC and anthropometry do not seem to be valid. Zimmermann et al (Zimmerman, et al, J Clin Endocrinol Metab, March 2013, 98(3):1271-1280), suggested that UIC in school-aged children be in the range of 100-299 µg/L to avoid both deficiency and excessive. Nevertheless, UIC from one casual urine is not adequate for defining % inadequacy or excessive. A forthcoming paper (in press in JN) demonstrated a need to correct for intra-variability in UIC to properly estimate the %prevalence of either ends.

The authors’ answer:

Indeed, it is a disadvantage of our study that UIC was used as a proxy of an individual iodine status. At present, WHO recommended UIC as the most practical biomarker for assessing iodine nutrition in a population (WHO, Assessment of the iodine deficiency disorders and monitoring their elimination, 2 edn, 2001), although not in individuals since it reflects recent iodine intake. However, low UIC probably reflect a prolonged low iodine status in an individual (Soldin OP, et al, Therapeutic drug monitoring, 2005, 27 178-185). In our study, a categorization in five UIC groups instead of using the continuous variable diminished the possible misclassification bias, due to daily variations of iodine intake. A Spain paper also divided maternal UIC into five groups to assess the association between maternal UIC and birth weight of their newborns (Alvarez-Pedrerol, et al, European Journal of Endocrinology, 2009, 160: 423-429). It has been discussed in the last paragraph of discussion.
b. Ref 37, paper from Bangkok referred to in the discussion: please consider the finding carefully. I do not have access to this paper, but from the abstract, it is not a supplementation trial. It seems to be data from the routine clinical service and the supported evidence was drawn from some thousand data points from clinical records. Please consider the references provided in the comments on results above.

The authors’ answer:

Ref 37, paper from Bangkok and the corresponding statement have been deleted from the discussion (e.g. Discussion section, line 198, page 6).

c. Is there clear evidence that iodine deficiency or excessive affect growth/anthropometric indicators? Given that the studied population of infants appears to be in the normal range for both anthropometry and UIC, the argument about the lowest means of anthropology was found in the UIC <50 and that of hyperthyroidism in infants may not be valid.

The authors’ answer:

Many studies have shown that iodine deficiency or excessive can affect growth and anthropometric indicators (e.g. Ref 16-19, 39-42). Although our infant and mothers were in general regarded as iodine adequate, there were still 2.7% of infants and 5.5% of mothers with UIC below 50, and 37.1% of infants and 19.3% of mothers with UIC above 300. Furthermore, there were a proportion of our infant with abnormal weight and height (HAZ or WAZ < -3).

6. Editorial: please kindly have a final edit of the MS and correcting typo errors.

The authors’ answer:

We carefully proof read the manuscript to correct the typographical, grammatical, and bibliographical errors.