Author's response to reviews

Title: Early feeding of larger volumes of formula milk is associated with greater body weight or overweight in later infancy

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Author’s response to reviews:

Response to Reviewers

Reviewer reports:

Reviewer #1: The study evaluated the relationship between volume of formula fed in early infancy and risk of overweight in later infancy. Using a prospective design, infants' milk records were collected at 3 months of age and body weight and length were measured at 5 time points from birth to 12 month of age. Compared to breastfed infants, infants who received high volumes of formula had significantly higher weight and lengths from 3 month to 12 months of age. The study concluded that feeding young infants high volumes of formula is associated with greater body weight and overweight in later infancy. The study addresses an important and interesting question; however, there are many issues that limit the paper's interoperability and impact.
Abstract

The abbreviation WLZ needs to be defined in line 39 instead of line 43. The abbreviation BAZ needs to be defined in the abstract.

Response: Thanks for your advice. We corrected them accordingly (line 39-40).

Introduction

Line 53: Change "growth and development of infants in infancy" to "growth and development in infancy"

Response: We corrected it accordingly (line 58).

Line 54: Please define and/or provide an example of feeding patterns. It seems that the manuscript looks at intake (volume and type of milk) not feeding patterns. Consider changing the terminology throughout the manuscript.

Response: We totally agree with you that the present study aim to investigate the volume and type of milk intake not feeding pattern(such as described in line 63). We changed the terminology throughout the manuscript except here because we need to indicate the association between feeding patterns and growth or risk of obesity has been studied extensively (lines 57-62). We provided an example of feeding patterns in the revised manuscript “Feeding patterns such as breastfeeding or formulas-feeding” (line 57).

Lines 60-62: The citation for the systematic review is missing.

Response: We added the citation in line 69.

Lines 60-73: This paragraph is a good summary of the literature; however, a topic (introductory) sentence and concluding sentence are needed to summarize and synthesize this information and connect it to the present study.

Response: We added a topic sentence as “The difference in weight gain between formula-fed and breast-fed infants is likely to be related to differences in both the composition and volume of intake between formula and breast milk.” in lines 65-67 and a conclusion sentence as “Therefore, feeding larger volumes of formula may be associated with greater body weight and length gains.” in lines 80-82.
Lines 74-75: This sentence is associated with the previous paragraph and should be moved. Please see suggestions for Lines 60-73.

Response: We moved it to the previous paragraph as a conclusion sentence. (lines 80-82)

Line 76: Please clarify which infant formula is a major public health problem in China.

Response: Indeed, the low-quality infant formula is a major public health problem in China but this is not the key point needed to be addressed in the present study, so we deleted this point in the manuscript.

Lines 74-81: This paragraph infers that the results of the study will only apply to the Chinese population. However, research on portion size (directly related to volume) has been shown to be consistent across various populations in both children and adults. I would reconsider how you connect the various ideas within this paragraph. Also, the information presented in Lines 74-77 to not obviously lead to the aim of the study presented in Lines 77-81. Overall, I would consider rewriting this paragraph and/or splitting it into 2 paragraphs.

Response: Thanks for your comments. We revised the paragraph as “The infant formula has been widely used in China over the last decade and about 65.3% infants aged within 6 mo has consumed infant formula. However, whether the large amount of formula intake in early infancy may contribute to the increased prevalence of overweight and obesity in later life has not been extensively studied. Thus......”(lines 83-86)

Materials and Methods

Lines 85-88: This sentence could be clarified to say "Using a population-based, prospective, observational study design, TMCHC collected detailed information on pregnant women and their infants to investigate the influence of nutrition intervention during pregnancy and infancy." Please provide a sentence about the nutrition intervention.

Response: We corrected this sentence accordingly (lines 94-97) and apologized for the misusage of the term “nutrition intervention” because the present study was a observational study not involved in nutritional intervention.

Lines 88-92: There seems to be a typo on Line 91 and thus this section should be two sentences.
Response: We corrected it in the revised manuscript (line 100).

Lines 93-108: The relationship between the sample selection methods used in the present study (Lines 93-108) and the overarching study (Lines 84-92). The description TMCHC study said that pregnant women (and therefore their infants) were enrolled in this study, but infants were screened for enrollment in the present study suggesting that the infants were not previously enrolled/connected to the study (Line 94).

Response: Sorry for the confusion. The data of the present study were collected from a subgroup of the Tongji Maternal and Child Health Cohort (TMCHC) study. Healthy neonates (n=1229) who were born between March 2014 and June 2015 from TMCHC and who were followed up with until 1 year of age were screened for enrollment in the present study. (lines 102-104). Those who were not born between March 2014 and June 2015 and who were not followed up with until 1 year of age were not included in the present study.

Lines 96-97: Also, why was 6.7% used as the estimated rate of overweight and obesity at 1 year of age? Please provide a rational and/or citation for this percentage.

Response: According to the data from China children nutrition surveillance in 2005, the overweight rate based on the WHO standards in urban area was 6.7%. We added the citation as reference [18] in the revised manuscript (line 107 and 367-368).

Lines 116-117: How was it determined that caregivers prepared the formula milk according to the instruction of manufacturers?

Response: We did not determined exactly how the caregivers prepared the formula milk. However, the caregivers was inquired about how to prepare the formula solution for infants at each interview by a community physician. Generally, the caregivers prepared the formula milk according to the instruction of manufacturers by using measurements provided by manufacturers. (lines 129-132)

Lines 117-119: Why were the volumes of formula consumption recorded by the community physician at their home visit with the intake reported by the caregivers in 100 formula-fed infants at age of 3 months? Were the 100 formula-fed infants in this study or a different study? If they were in this study, please describe how you selected these 100 infants? If they were in a different study, please provide a reference.
Response: We described this point in the revised manuscript as “To verify the volume of formula consumption provided by the caregivers, we compared the volume of formula consumption recorded by community physician at their home visit with the intake reported by the caregivers in randomly selected 100 formula-fed infants at the age of 3 mo in the present study.” (lines 132-135)

Lines 119-120: Does "the quantities" refer to the quantities consumed by the 100 formula fed infants (Line 119) or all the infants in the study? Please clarify this point. Also, please cite the two independent reports.

Response: We clarified this point in the revised manuscript as “The quantities are comparable in two independent reports recorded by community physician and the caregivers for 100 infants.”(lines 135-137)

Lines: 120-121: Do "the two independent reports" refer to the Chinese infant feeding recommendations and references to the dietary intake of Chinese residents? I would not call these two sources reports as feeding recommendations typically provide guidance not information on what is actually being consumed.

Response: Sorry for the confusion. We clarified this point as above described.(lines 135-137)

Lines 120-124: The cut-off point of 840 mL seems to be based on three different sources of information: Chinese infant feeding recommendations, references to the dietary intake of Chinese residents, and the average formula consumption of the infants in this study. It seems odd that all of these sources of information aligned exactly at 840 mL as a cut-off point. Please clarify and provide more discussion on how this cut-off point was determined.

Response: Chinese infant feeding guideline recommend that all infants should be exclusively breastfed in the first six months of life. However, for the formula-fed infants, according to the references to the dietary intake of Chinese residents and composition of formulas, the 3-month-old infants consume an average of 140 ml of formula 6 times/d for a total of 840 ml/d. This cut-off point was about P75 intake of formula in the formula-fed infants in the present study.(lines 138-141)

Line 129: Please define mixed feeding and artificial feeding.
Response: We revised this point as “Formula feeding included any formula feeding with or without some breast milk.” (lines 146-147)

Line 135-137: From what I understand, you calculated the z score of the difference between WLZ and BAZ from birth to 1 mo, 1 to 3 mo, 3 to 6 mo, and 6 to 12 mo. Why was a z score of the difference between the z scores calculated? Why wasn't the difference/change between the z scores used? Please explain more and clarify this point.

Response: Sorry for the mistake, we corrected it in the revised manuscript as “To assess longitudinal growth, interval growth changes between 3 feeding groups were determined by obtaining the differences in WLZ and BAZ” (lines 153-154), not “the z score differences in WLZ and BAZ”

Line 138: Why was greater body weight included? Was it meant to represent "at-risk for overweight"? Also, I suggest changing "nutritional status" to "weight status" and continue this change throughout the paper. As an obesity researcher, I have never seen weight-for-length or BMI-for-age z scores called nutritional status within the obesity literature.

Response: We used greater body weight (1SD<WLZ≤2SD) because it represented at-risk for overweight (line 156). We replaced "nutritional status" with "weight status" throughout the paper.

Other questions about methods: Why was formula intake (mL) not analyzed as a continuous variable? How was the volume of breastmilk determined? Also, I do not think the 1 month time point is important for this study and should be excluded from methods and results.

Response: The volume of formula intake was not analyzed as a continuous variable but analyzed as categorical variables because the volume is 0 for breast-fed infants. We did not determine the volume of breastmilk consumption in the present study, so we did not analyze the individual energy intake. We discussed this point as limitation (line 280). We agreed with you and excluded the data for 1 month time point.

Results

Lines 163-164: Should this exclusion criteria be included with the other exclusion criteria presented in an earlier paragraph in the paper (Paragraph in Lines 93-108).
Response: We clarified the exclusion criteria in the method section.(lines 122-123)

Line 164: I did not see a clear list of inclusion criteria. Please clarify the exclusion criteria in your methods section.

Response: The inclusion criteria(lines 102-104) and exclusion criteria (lines 122-123) were described in the method section of revised manuscript.

Lines: 167-169: P values are missing for these results. Please add.

Response: We added P values in the revised manuscript.(lines 186-190)

Line 171: Why was the % of breastfed female infants presented? What about the formula-fed infants?

Response: To compare the percentage of female in breastfed infants with the other groups, we list the % of female infants. We clarified this point in the revised manuscript as “With respect to the sex of the infants, 50.5% of the breastfed infants were female, more than that of LFM infants (42.4%) or HFM infants (38.3%)(p<0.01).”(lines 189-190)

Lines 173-175: P values are missing for these results. Please add.

Response: We added P values in the revised manuscript.(lines 197-199)

Line 177: Does "continued until 12 mo of age" mean that differences in body weight and length between the HFM and BM infants was significantly difference at both 6 and 12 months of age? If this is true, this point needs to be clarified.

Response: We clarified this point in the revised manuscript”The average values of body weight and length at three time points were greater in infants in the HFM group than those in the BM groups(p<0.05 or p<0.01), but there was no significant difference between infants in the LFM and BM group except those at 12 mo (p<0.001).”(lines 191-195). And, we added the description about the result of WLZ and BAZ.(lines 197-199)
Lines 187-189: From what I understand, WLZ and BAZ changes did not change in the LFM and HFM groups; whereas, WLZ and BAZ decreased in the BM group. However, these differences were not statistically significant. Is this correct? Also, please add the p values to this result.

Response: Yes, it is correct. From 6 to 12 mo of age, WLZ and BAZ did not change in the LFM and HFM groups (values of change closed to zero), WLZ and BAZ changes decreased in the BM group (values of change were -0.19 and -0.16). However, the difference was only statistically significant in WLZ change. We added the p values in the Table 3.

Lines 193-195: These confounders were listed in the Statistical Methods section and thus do not need to be listed again.

Response: We deleted them accordingly.

Lines 196-202: P values are missing for these results. Please add.

Response: We added the P values in the revised manuscript (lines 219-221) and Table 4.

General comment: Birth height and weight were only used as control variables and thus the relationship between volume of formula and growth measures at baseline should not be reported in results, tables, or figures.

Response: We considered your suggestion and agreed with you that birth height and weight were only used as control variables, but we kept these data in the results to provide more information at baseline and to clarify the relationship between volume of formula and growth measures in the follow-up.

Discussion

General comment: Overall, there are issues with word usage, verb tense, and sentence structure throughout this section. I suggest closely editing this section to resolve these issues and improve clarity. This applies to the conclusion too. Also, the results section evaluates the primary aim of the study in three ways; however, there is no discussion about why the results of each analysis differed slightly. Please add this in the discussion.

Response: We apologize for the problems. The manuscript has been thoroughly edited by American Journal Experts and again by a native English speaker. We attempted to correct all
mistakes and improve the writing as possible as we can. We added the discussion about the results in the revised manuscript.(lines 227-232)

Line 208: Add that this result I the comparison of lower-volume formula feeding and breastmilk.
Response: We added the discussion about the results in the revised manuscript.(lines 227-230)

Lines 209-211: This sentence could be clarified. For example, "These findings are consistent with previous studies that demonstrated that growth in infancy may be affected by the type and volume of milk fed." As previously mentioned, I do not think "feeding patterns" is the correct terminology for this study.
Response: We agreed with you and corrected the sentence accordingly(lines 230-232).

Line 218-219: Instead of "decrease their ability to self-regulation of milk intake", I think "lose their ability to self-regulate intake" is clearer. Also, children do not develop a satiety response and appetite regulation, they are born with these abilities. Thus, "delay in development" is not appropriate.
Response: We corrected them accordingly(lines 240-242).

Line 220-223: As previously mentioned, how was the volume of breastmilk determined? Please provide these details in the methods section.
Response: We did not determine the volume of breastmilk consumption in the present study, so we did not analyze the individual energy intake. This point was the limitation of our study, as discussed in the revised manuscript.(line 280)

Line 224: How was the energy content of the formula determined and how did you determine if formulas were prepared correctly by mothers/parents in the study? If you are confident in the energy content of both the breastmilk and formulas, why was the relationship between energy and weight not determined in this study?
Response: We did not determined exactly how the caregivers prepared the formula milk. However, the caregivers was inquired about how to prepare the formula solution for infants at each interview by a community physician. Generally, the caregivers prepared the formula milk
according to the instruction of manufacturers by using measurements provided by manufacturers. As described in the revised manuscript” To verify the volume of formula consumption provided by the caregivers, we compared the volume of formula consumption recorded by community physician at their home visit with the intake reported by the caregivers in randomly selected 100 formula-fed infants at the age of 3 mo in the present study. The quantities are comparable in two independent reports recorded by community physician and the caregivers for 100 infants.”(lines 132-137). We did not determine the individual energy intake in the present study. But previous studies reported that the energy content of conventional formula milk (67 kcal/100 ml) was higher than breast milk (65 kcal/100 ml)([13])

Lines 277-247: This paragraph needs to be split into multiple paragraphs. There are currently too many ideas that are not discussed enough.

Response: We deleted the discussion on European multicenter double-blind randomized clinical trial because this study raised another question which not related to the present study.

Line 227-230: This sentence would be clearer and less wordy if rewritten as two sentences.

Response: We separated this sentence to two in the revised manuscript “Another possible explanation is related to “the early protein hypothesis”, which postulate that differences in protein supply between human milk and infant formula play an important role in early programming. This hypothesis assume that more protein intake is causative for a more rapid weight gain.(lines 250-253)”

Line 244: Please define "modern formula."

Response: We deleted the discussion on this point in the revised manuscript.

Line 252-253: It is inferred that a prospective study is longitudinal; thus, you do not need both descriptors.

Response: We agreed with you and deleted the word “longitudinal”(line 267).
Conclusions

Lines: 276-278: I am not sure how the study concluded that "these findings provide evidence-based guidelines of reasonable feeding" Also, I do not know what "reasonable feeding" means.

Response: We revised this point as “Thus, the higher-volume formula feeding should be avoided in the early infancy to prevent overweight or obesity in later infancy.” (lines 289-290)

Tables 3 and 4: It would be helpful if P values were provided in the tables for all results. Also, I am not sure why heights and weights are included in the tables as the relationship between milk intake and growth measures was only looked at after 3 months of age. I would remove these (i.e., time points less than 3 months) from the tables as you don't know the infants' intake before 3 months of age.

Response: We added the p values in the revised Table 3 and Table 4. We excluded the data for 1 month time point from the results but kept the baseline data at birth.

Figure 2: Also, I am not sure why WLZ and BAZ birth and 1 month as the primary aim of the study could not be evaluated until after 3 months of age. I would remove these (i.e., time points less than 3 months) from the tables as you don't know the infants' intake before 3 months of age.

Response: We excluded the data for 1 month time point from the results but kept the baseline data at birth.

Reviewer #2: The paper entitled: "Early feeding of larger volumes of formula milk is associated with greater body weight or overweight in later infancy" is interesting and well written.

The authors present results of a prospective observational study performed on a large cohort of infants. They compare growth data between formula-fed infants receiving higher vs. lower volumes of formula at 3 months of age. They present also growth data from breastfed infants as a reference group.

In fact it is not a new idea that the volume of formula consumed influences an infant's growth. The most important limitation of the study is lack of data on energy consumption.
However, I recommend this paper to be published as there are some interesting points raised:

- descriptive analysis of factors influencing different feeding patterns

- demonstration, that feeding patterns in general, particularly volume overfeeding in early infancy may potentially predispose a child for future overweight

- results of linear mixed-effect modelling

The study would have more impact if longer term growth data, beyond infancy, were reported and possibly a programming effect demonstrated (or not).

Response: Thanks for your positive comments and great advice.

Abstract:

- One would expect explanation of abbreviations (WAZ and BAZ)

Response: we added the full spellings for abbreviations WAZ and BAZ (lines 39-41)

Background:

- No major remarks

Methods:

- The authors do not explain how the anthropometric data were obtained (staff, equipment, quality of data obtained)

Response: we detailed the information in the revised manuscript as “Body weight and length was measured by the trained community physician. Body weight was measured to the nearest 100 g using a pedobarometer, with infants wearing light indoor clothing. Recumbent length was measured to the nearest 0.1 cm using an infantometer. Both weight and length were taken in duplicate and means of the replicates were recorded.”(lines 116-120)

Results:

- No major remarks
Discussion:

- No major remarks

- The sentence on page 9 (line 217-218) not clear enough

Response: we revised the sentence as “Rapid growth in early infancy had been shown to increase the risk of overweight or obesity during later life, which conformed to our findings that higher-volume formula feeding contributed to greater body weight and body length, and more change in WLZ and BAZ from 3 to 6 months of age, thus increased risk of overweight in later infancy.” (lines 234-236)

Conclusions

- No major remarks

References

- Adequate and up to date

Figures

- Clear and well designed

Tables

- Table 1: Please, add "(\%)" in maternal age characteristics. I’d also skip the second line ("no") in case of parameters, where only "yes" or "no" is possible. This could make the table a little bit shorter

Response: we revised accordingly in Table 1.