PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Infant BMI Peak as a predictor of overweight and obesity at age 2 years in a Chinese community-based cohort
AUTHORS	Sun, Jie; Nwaru, Bright; Hua, Jing; Li, Xiaohong; Wu, Zhuochun

VERSION 1 - REVIEW

REVIEWER	Jianduan Zhang Huazhong University of Science and Technology
REVIEW RETURNED	22-Jan-2017

GENERAL COMMENTS	Childhood obesity has become a serious public health issue in China. The authors investigated infant peak BMI and its association with overweight and obesity at aged two; and the study addresses an important and current theme. In general the paper was well written but there were some important areas, which need to be addressed and improved. Below are my specific comments: 1. Through out the paper, when the value of BMI at its peak was discussed, instead of using BMI peak, the term of peak BMI should be used. While the timing was addressed, BMI peak can and shall be used. For example, the title of Table 5 should be 'Association between infant peak BMI (not BMI peak) and overweight and obesity at age 2 years'. 2. The authors used a term of BMI peak trajectory, which is confusing. Could a peak have Da trajectory? If so, could the authors present the trajectory in a more straightforward and visualized way, i.e., a plot graph showing the trajectory? 3. As the authors indicated in the paper, the BMI trajectory might be ancestry-specified, would it be suitable to use the inclusion criteria set by the CHOP study in Philadelphia, USA as indicated in page 4, line 25-33? 4. A typo in Page 6, line 12, "not inestimable" should be inestimable?

REVIEWER	Izzuddin M Aris Singapore Institute for Clinical Sciences Singapore
REVIEW RETURNED	11-Feb-2017

GENERAL COMMENTS	The authors have investigated the causes and effects of the location (age and magnitude) of the BMI peak in early childhood, using data from a community-based longitudinal cohort in China. BMI peak has received much interest recently as a potential predictor of future obesity and metabolic risk, and this study makes an important contribution in understanding the role of early BMI development in Asian populations. However, there are a few methodological

	considerations that the authors would need to address. Major comments: 1) I am not convinced that the authors' have made the appropriate choice in the statistical model used in estimating BMI peak from BMI trajectories. Conventional polynomial models, as the one described in the paper, can be misleading as it encompasses relatively few curve shapes and are highly inflexible. There exist better alternatives to this technique, such as the more flexible fractional polynomial models or natural cubic spline models. Both have been shown to be more parsimonious than conventional polynomials, with at least equal, or better fit to the data. 2) Analysis of repeated measures, such as BMI at multiple timepoints, needs to take the correlation between repeated observations on the same person into account, and this is commonly performed by utilizing multi-level regression models, which analyse repeated measures clustered within individuals, as fixed and random effects. The authors mentioned that "regression modelling was used for each child…", but it is unclear if they used multi-level models to derive individual-specific BMI trajectories, which is an important component in BMI peak estimation. 3) It would be better/more powerful to add variables like sex, delivery mode etc and their interactions with age into the model, than to exclude them and produce BMI curves only as a function of age. The first approach explicitly models the relationship of sex, delivery mode etc with the sample average curve, and by modelling this between-individual variation, the within-individual variation (i.e., error) will reduce 4) The BMI peak is an estimation and not the true peak. Please add a comment to the discussion about this. In addition, could this lead to bias in the second stage when estimating the association between BMI peak and overweight at age 2 years? 5) I am concerned regarding the attrition rate of this study. Only 21.2% (2268/7456) of the infants were eligible for analysis, which poses a potentially huge selection bias. Were the "ineligible" infants fatter or more overweight/obese to begin with? Were there disproportionately more males than females, or more infants with birthweight > 4kg in the "ineligible" group? It would be helpful if the authors could provide some sort of comparison between the "eligible" and "ineligible" infants to highlight any baseline differences between these two groups. Minor comments: 1) Abstract: The objectives need to be more specific and stated more clearly, in terms of assessing the predictors and effects of infant BMI peak characteristics. 2) Abstract (Results): It is unclear what "higher" later timing and magnitude refers to. Higher by 1 month / 1 kg/m2? Higher by 1 SD? Please specify 3) Introduction: Please use a more recent reference on the prevalence of overweight/obesity in children. (e.g., the WHO report on Commission on Ending Childhood Obesity, released in 2016)

	4) Introduction: The authors should present a more holistic introduction that considers the reasons why infant BMI-cardio-metabolic risk associations may not exist or may be driven by traits other than adiposity (e.g., length/height and fat-free mass), as well as why they may exist 5) Methods: How was the fit of the model assessed? Residual plots? AIC (or BIC)? The authors need to provide more information on this in the Methods. The mean R2 value is not a reasonable metric for assessing model fit, as the authors allude to in the Results. 6) Methods: Please provide a more detailed description on how the magnitude and timing of BMI peak were calculated for each subject from the model 7) Methods: Please elaborate on why BMI at 14 days of age was chosen as the "baseline" in estimating the velocity to the peak, when data at birth was available which would have made a better "baseline" 8) Strictly speaking this study is a community-based, and not a population-based study. The authors should amend the terms "population-based" to "community-based" where relevant in the manuscript 9) Methods: Elaborate on the reasons for excluding preterms in the study 10) Methods: The authors mentioned that "Participants were also eligible if they had at least six measurements of height and weight in the first 13.5 months of life". This is confusing, as the data was collected at 1, 2, 4, 6, 9, 12 and 18 months. Where did the 13.5 months come from? Please elaborate 11) Methods: Please provide information regarding the reliability of the anthropometric measurements (inter-observer technical error of measurements, coefficient of variation etc) 12) Methods: Did all community centres use the same instruments for measuring weight and length? 13) Methods: Please elaborate on how breastfeeding data was collected. Were they administered per WHO guidelines? 14) Methods: Please elaborate on how sleeping data was collected 15) Methods: It is much better to use birthweight as birthweight-for-gestational age z-scores, rather than categorizing them. There is currently a WHO reference for birthweight-for-gestational age that is available that can be implemented easily 16) Results: The correlations between the estimated BMI peak characteristics (timing, magnitude and velocity to BMI peak) need to be reported, and if they are substantial, it calls into question the results of Table 5. 17) Discussion: As the data is based primarily in children living in urban areas, please add comment on the potential generalizability of the study findings, given the known rural-urban differences in child

	BMI and prevalence of overweight/obesity 18) The paper needs to be edited by someone with a proficiency for the English language

REVIEWER	Loredana Marcovecchio University of Cambridge, UK
REVIEW RETURNED	30-Apr-2017

GENERAL COMMENTS	The objective of this study was to characterize infant BMI trajectories in Chinese longitudinal cohort of around 2000 children and investigate the relationship between the infancy BMI trajectory and childhood obesity at the age of 2 years. The study is of interest given that it is the first exploring the specific research question in the Chinese population. However the study presents several limitations. 1. The description of the study population should be more accurate, by reporting more details on inclusion and exclusion criteria 2. The term ‘Length’ should be used instead of ‘height’ throughout the manuscript. Please specify the method used to assess length. At present only methods for weight assessment are reported. 3. Why only data for the BMI curves until 13.5 months were included? 4. No prenatal or perinatal history was collected. Any information on maternal gestational diabetes? 5. The 95th percentile for BMI corresponds to 1.64 z-score. Why the authors used 2 z-scores as cutoff? 6. Weight z-score instead of raw data should have been calculated at birth and used in the analysis 7. The results presentation needs to be improved. The authors should report a figure showing BMI trajectories, given that this was a part of the primary analysis 8. There are several missing variables which should have been considered, such as feeding, gestational diabetes, maternal smoking, as well as prenatal and perinatal data. 9. Are the results for birth weight on table 5 correct? 10. Overall the discussion needs to be improved. The study findings need to be better commented. In addition, the authors should comment the clinical relevance of the small differences in age and magnitude of peak BMI between boys and girls. The statistical significance is related to the large sample size 11. Tables 1 and 2 are not necessary

REVIEWER	Jenny M Kindblom Institue of Medicine, University of Gothenburg, Sweden
REVIEW RETURNED	05-May-2017

GENERAL COMMENTS	This is a well-motivated study of the infancy BMI peak and its association with overweight/obesity at 2 years of age in a Chinese cohort. The authors present descriptive statistics of the BMI peak and the associations between the BMI peak and the increased risk of overweight and obesity at 2 years of age. Their main result is that higher and later BMI peak was associated with increased risk of overweight /obesity at age 2 years.

	I have three major concerns about this study: 1. The inclusion process of the subjects needs to be clarified. As described in the Methods section, the cohort started off with 10,674 infants and ended up with 1,949 infants included in the study. This results in only 18% included subjects from the original population-based cohort and a high risk of selection bias. I suggest: a. To clarify the inclusion criteria, with the removal of “also” line 27 page 4. b. To include a figure of the inclusion process with n-numbers for the different exclusions steps, and the actual number of included subjects, to illustrate the inclusion process. c. To be consequent in the reporting of the percentage and n-numbers of included subjects (Abstract, Methods section, the second paragraph in the Discussion section, and Tables). There are different n-numbers in the abstract, the methods and the tables, which is confusing. d. To address this possible selection bias in the discussion as a limitation of the study, and also the results of the association need to be toned down. 2. The statistical analyses in the Methods section needs to be clarified. Define the variables (magnitude and timing of BMI peak, BMI peak, velocity to peak) and specify which covariates are included in table 5 so that this information is available in table 5 3. I am also concerned that there might be a potential selection bias due to that there are more large-at-birth infants with inestimable peak BMI. Since infants with higher birth weight was inestimable to a higher extent than infants with low or normal birth weight, it might have implications of the results for the association analysis given that birth weight is associated with peak BMI and childhood overweight and obesity. I suggest to add an analysis of overweight and obesity under the title “General characteristics of children at age two years” page 8. Minor comments: 1. Abstract/Objectives: Insert “populations” after European (line 12). 2. Abstract/Objectives: Add the second aim, to investigate the association between infant BMI peak and overweight/obesity at 2 years of age. 3. Abstract/Methods: Is n=2073 valid? See major comment 1. 4. Abstract/Methods: Is there a difference between higher infant BMI peak and higher magnitude of infant BMI peak? Please specify. 5. Abstract overall: Insert “at age 2 years” after childhood overweight/obesity on at least one occasion. 6. Line 15, page 4. “…the missing of the subjects”, replace with “…loss to follow-up”. 7. Why was the interval 14-408 days chosen as to where the BMI peak should occur? Please provide a rationale. 8. Table 2 should be removed and the information of the covariates should be added to the table text in Table 5. See major comment 2. 9. Table 5 table text, include which analyses that have been used. 10. Table 5, the OR and 95% CI for birth weight are odd.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Jianduan Zhang
Institution and Country: Huazhong University of Science and Technology
Please state any competing interests: None declared

Please leave your comments for the authors below

Childhood obesity has become a serious public health issue in China. The authors investigated infant peak BMI and its association with overweight and obesity at aged two; and the study addresses an important and current theme. In general the paper was well written but there were some important areas, which need to be addressed and improved. Below are my specific comments:

1. Through out the paper, when the value of BMI at its peak was discussed, instead of using BMI peak, the term of peak BMI should be used. While the timing was addressed, BMI peak can and shall be used. For example, the title of Table 5 should be 'Association between infant peak BMI (not BMI peak) and overweight and obesity at age 2 years'.
R: Thank you for this suggestion. We have now specified this as follows: BMI peak characteristics [age (in months) and magnitude (BMI; in kg/m2) at peak and pre-peak velocities(in kg/m2/month] were estimated.

2. The authors used a term of BMI peak trajectory, which is confusing. Could a peak have Da trajectory? If so, could the authors present the trajectory in a more straightforward and visualized way, i.e., a plot graph showing the trajectory?
R：We apologize for this error and we have corrected it as BMI trajectory. Thank you for suggesting we present a graph. We've added the Figure 2 and Supplemental Figure 1 to show the trajectory.

3. As the authors indicated in the paper, the BMI trajectory might be ancestry-specified, would it be suitable to use the inclusion criteria set by the CHOP study in Philadelphia, USA as indicated in page 4, line 25-33?
R: We thank the reviewer for this helpful comment. There are two articles（reference19, 23）referring to the European and American BMI peak curves using this standard. Other selection criteria are also similar, for example, only full-term children were recruited. In order to compare with the European and American populations'curves, we took the same criteria into consideration.
19. Roy SM, Chesi A, Mentch F, Xiao R, Chiavacci R, Mitchell JA,et al. Body Mass Index (BMI)Trajectories in Infancy differ by population ancestry and may presage disparities in early childhood obesity. J ClinEndocrinolMetab 2015;100:1551-1560.
23.Wen X, Kleinman K, Gillman MW, Rifas-Shiman SL, Taveras EM. Childhood body mass index trajectories: modeling, characterizing, pairwise correlations and socio-demographic predictors of trajectory characteristics. BMC Med Res Methodol 2012;12:38.

4. A typo in Page 6, line 12, “not inestimable” should be inestimable?
R: Thank you for this suggestion. We have now changed this as suggested. (Page 7, line 39.)

Reviewer: 2
Reviewer Name: Izzuddin M Aris
Institution and Country: Singapore Institute for Clinical Sciences, Singapore
Please state any competing interests: None declared

Please leave your comments for the authors below

The authors have investigated the causes and effects of the location (age and magnitude) of the BMI peak in early childhood, using data from a community-based longitudinal cohort in China. BMI peak has received much interest recently as a potential predictor of future obesity and metabolic risk, and this study makes an important contribution in understanding the role of early BMI development in

Asian populations. However, there are a few methodological considerations that the authors would need to address.

Major comments:

1) I am not convinced that the authors' have made the appropriate choice in the statistical model used in estimating BMI peak from BMI trajectories. Conventional polynomial models, as the one described in the paper, can be misleading as it encompasses relatively few curve shapes and are highly inflexible. There exist better alternatives to this technique, such as the more flexible fractional polynomial models or natural cubic spline models. Both have been shown to be more parsimonious than conventional polynomials, with at least equal, or better fit to the data.
R: Thank you for your suggestion. Though from the perspective of statistical modeling, we should really choose the appropriate model such as natural cubic spline model. We have verified that the natural cubic spline model did show results that are more suitable than the polynomial model. It is possible that different modeling methods used to derive BMI peak characteristics could account for the observed differences across populations. In order to compare with other populations, we used a polynomial model that was consistent with other article(reference 19).We agree that this is an important area that requires further research.

2) Analysis of repeated measures, such as BMI at multiple time points, needs to take the correlation between repeated observations on the same person into account, and this is commonly performed by utilizing multi-level regression models, which analyse repeated measures clustered within individuals, as fixed and random effects. The authors mentioned that "regression modeling was used for each child…", but it is unclear if they used multi-level models to derive individual-specific BMI trajectories, which is an important component in BMI peak estimation.

R: Based on your suggestion, we re-validated the multi-level model and found that the results were very close to the simple model used in the current manuscript. In this manuscript, for each subject, a polynomial regression model with quadratic terms was fit to the BMI measurements over time. That is, for each child, regression modeling was used to fit the following equation:
$BMI = \beta_0+[\beta_1 * (\text{age in days})] + [\beta_2 *(\text{age in days})2]$
Using the subject-specific coefficients derived from the model, magnitude and timing of BMI peak and velocity to peak were defined for each subject.
3) It would be better/more powerful to add variables like sex, delivery mode etc and their interactions with age into the model, than to exclude them and produce BMI curves only as a function of age. The first approach explicitly models the relationship of sex, delivery mode etc with the sample average curve, and by modelling this between-individual variation, the within-individual variation (i.e., error) will reduce

R:We follow these suggestions to put these variables into a multi-level model for control, the calculated BMI peak and time show no difference with current outcome.

	Peak BMI	Age(month)
Total(n=2073)	18.15	7.63
Adjusted for Gender and Cesarean section	17.97	7.63
Gender		
Male	18.40	7.59
Female	17.90	7.69
Total (n=7456)	18.12	7.58

Adjusted for Gender
and Cesarean section 17.96 7.58
Gender
Male 18.37 7.50
Female 17.87 7.66
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4) The BMI peak is an estimation and not the true peak. Please add a comment to the discussion about this. In addition, could this lead to bias in the second stage when estimating the association between BMI peak and overweight at age 2 years?
R:Thank you for this suggestion. We will modify the discussion according to your suggestion (Page11 Line47). We compared the BMI value measured at six months and nine months with BMI peak estimated by polynomial or natural cubic spline models. It is found that the ROC area of BMI peak by polynomial models is the best. It can explain the change of the whole population and compare it among the people.

Area Under the Curve
Test Result Variable(s) ROC Area
BMI peak by polynomial models 0.831
6 months BMI 0.786
9 months BMI 0.814
BMI peak by natural cubic spline models 0.802

5) I am concerned regarding the attrition rate of this study. Only 21.2% (2268/7456) of the infants were eligible for analysis, which poses a potentially huge selection bias. Were the “ineligible” infants fatter or more overweight/obese to begin with? Were there disproportionately more males than females, or more infants with birth weight> 4kg in the “ineligible” group? It would be helpful if the authors could provide some sort of comparison between the “eligible” and “ineligible” infants to highlight any baseline differences between these two groups.
R：Thank you for this suggestion.To assess potential selection bias, we compared demographics and birth characteristics of the analytic sample(n=2268) to the excluded healthy singleton infants (n=4806). There were no substantial differences in sex, birth weight, maternal age or overweight and obese rates at age 2 years of the two samples. We have now changed this as suggested. (Supplemental Table 1)
Minor comments:

1) Abstract: The objectives need to be more specific and stated more clearly, in terms of assessing the predictors and effects of infant BMI peak characteristics.
We have corrected it in the abstract:
The utility of infant BMI peak for predicting childhood obesity has not been assessed in China. We aimed to characterize infant BMI trajectories in a Chinese longitudinal cohort and to evaluate whether BMI peak predicts overweight and obesity at age 2 years.

2) Abstract (Results): It is unclear what “higher” later timing and magnitude refers to. Higher by 1 month / 1 kg/m2? Higher by 1 SD? Please specify
R: It’s really a good suggestion. We have corrected it as follows:
R: With the peak BMI value increasing by 1 kg/m2 or the peak time by 1 month the risk of overweight at age 2 years increased by 2.11 times (OR 3.11; 95% CI 2.64-3.66) and 35% (OR 1.35; 95% CI 1.22-1.50) respectively.

3) Introduction: Please use a more recent reference on the prevalence of overweight/obesity in

children. (e.g., the WHO report on Commission on Ending Childhood Obesity, released in 2016)
R:Thank you for this suggestion. We have added data as suggested.(page 2, line 28）.
Reference from http://www.who.int/end-childhood-obesity/news/launch-final-report/en/
4) Introduction: The authors should present a more holistic introduction that considers the reasons why infant BMI-cardio-metabolic risk associations may not exist or may be driven by traits other than adiposity (e.g., length/height and fat-free mass), as well as why they may exist
R:Thank you for this suggestion. We have now changed this as suggested. （page 2, line 55.）
It’s reported that even a modest reduction in BMI z-score after one year of obesity intervention was associated with improvement in several cardiovascular risk factors. In young children, waist-to-height-ratio (WHtR) is not superior to BMI in estimating body fat percentage , nor is WHtR better correlated with cardio-metabolic risk factors than BMI in overweight/obese children. One study in Singapore suggests an important impact of early BMI development on later metabolic outcomes in Asian populations.
5) Methods: How was the fit of the model assessed? Residual plots? AIC (or BIC)? The authors need to provide more information on this in the Methods. The mean R2 value is not a reasonable metric for assessing model fit, as the authors allude to in the Results.
R: We did the fitting test for each curve separately and we could only use the mean of residual to explain. AIC or BIC was only in a multi-level model, so it is not described in the manuscript.

6) Methods: Please provide a more detailed description on how the magnitude and timing of BMI peak were calculated for each subject from the model
R: Thank you for this suggestion. We have now changed this as suggested.（page 6, line 42.）

7) Methods: Please elaborate on why BMI at 14 days of age was chosen as the “baseline” in estimating the velocity to the peak, when data at birth was available which would have made a better “baseline”
R: We considered BMI data between 14 and 408d of age to allow for a time lag before the outcome ascertainment (at 2 y) and to avoid the period of neonatal weight loss seen in the first 2 week of life.（Reference21）
8) Strictly speaking this study is a community-based, and not a population-based study. The authors should amend the terms “population-based” to “community-based” where relevant in the manuscript
R: Thank you for this suggestion. We have now changed this as suggested. （page 1, line 4.）

9) Methods: Elaborate on the reasons for excluding preterms in the study
R: The premature infants have the characteristics of catch-up-growth curve which will be confused with normal term children. To compare with the peak BMI of other populations, we take the similar criteria for excluding preterms in the study.

10) Methods: The authors mentioned that “Participants were also eligible if they had at least six measurements of height and weight in the first 13.5 months of life”. This is confusing, as the data was collected at 1, 2, 4, 6, 9, 12 and 18 months. Where did the 13.5 months come from? Please elaborate
R:There are two articles(Reference19,23) making 13.5m as a cut-off time. Some children's physical examination time may also be delayed for one months, so that more samples can be included in the study.

11) Methods: Please provide information regarding the reliability of the anthropometric measurements (inter-observer technical error of measurements, coefficient of variation etc)
Response: This is a very good proposal. However, we could not follow these requirements because our research is a retrospective study. In the future, we will follow your suggestion in a prospective cohort study.

12) Methods: Did all community centres use the same instruments for measuring weight and length?

R: All five community centers are administrated by Jing’an Maternal and Child Health Center , so they have the same type of instruments.

13) Methods: Please elaborate on how breastfeeding data was collected. Were they administered per WHO guidelines?
R: Parents recalled to feeding and sleeping questions in follow-ups. They reported the age in months at which breastfeeding was stopped. They were not administered by WHO guidelines.
14) Methods: Please elaborate on how sleeping data was collected
R: Sleep duration in hours was recorded at age 2 years.

15) Methods: It is much better to use birthweight as birthweight-for-gestational age z-scores, rather than categorizing them. There is currently a WHO reference for birthweight-for-gestational age that is available that can be implemented easily
R: Thank you for this suggestion. We derived birthweight-for-gestational-age z-scores using references from International standards for newborn.(Reference 29).
International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project
https://intergrowth21.tghn.org/global-perinatal-package/intergrowth-21st-comparison-application/

16) Results: The correlations between the estimated BMI peak characteristics (timing, magnitude and velocity to BMI peak) need to be reported, and if they are substantial, it calls into question the results of Table 5.
R: The correlations between the estimated BMI peak characteristics has been listed as Supplemental Table2. The empirical judgment method shows that when 0<vif

Model Collinearity Statistics
Tolerance VIF
Magnitude 0.575 1.739
Velocity 0.570 1.754
Age of BMI peak0.988 1.012

17) Discussion: As the data is based primarily in children living in urban areas, please add comment on the potential generalizability of the study findings, given the known rural-urban differences in child BMI and prevalence of overweight/obesity
R: Thank you for this suggestion. Prevalence of overweight and obesity has increased in both rural and urban China. We have now changed this as suggested.(Reference 30)

18) The paper needs to be edited by someone with a proficiency for the English language
R：I’m sorry for my poor English. Due to limited time, the modification of English is relatively simple.

Reviewer: 3
Reviewer Name: LoredanaMarcovecchio
Institution and Country: University of Cambridge, UK
Please state any competing interests: None to declare

Please leave your comments for the authors below

The objective of this study was to characterize infant BMI trajectories in Chinese longitudinal cohort of around 2000 children and investigate the relationship between the infancy BMI trajectory and childhood obesity at the age of 2 years.

The study is of interest given that it is the first exploring the specific research question in the Chinese population.
However the study presents several limitations.
1. The description of the study population should be more accurate, by reporting more details on inclusion and exclusion criteria
R: Thank you for this suggestion. We have now changed this as suggested. （page 5, line 20）

2. The term ‘Length’ should be used instead of ‘height’ throughout the manuscript. Please specify the method used to assess length. At present only methods for weight assessment are reported.
R: Thank you for this suggestion. We have now changed this as follows:
Recumbent length was measured from the top of the head to soles of feet using an infant mat to the nearest 0.1 cm .

3. Why only data for the BMI curves until 13.5 months were included?
R: There are two articles (Reference19,23) making 13.5m as a cut-off time. Some children's physical examination time may also be delayed for one months, so that more samples can be included in the study.

4. No prenatal or perinatal history was collected. Any information on maternal gestational diabetes?
R: This is a very good proposal. However, we could not follow these requirements because our research is a retrospective study. We have already elaborated on this limitation in the discussion section. At present, we have collected these information in an obesity intervention study.

5. The 95th percentile for BMI corresponds to 1.64 z-score. Why the authors used 2 z-scores as cutoff?
R:We apologize for this error, and we have corrected it as BAZ>+2 (BMI >97th percentile).

6. Weight z-score instead of raw data should have been calculated at birth and used in the analysis
R: Thank you for this suggestion. We derived birthweight-for-gestational-age z-scores using references from International standards for newborn.(Reference 29).

7. The results presentation needs to be improved. The authors should report a figure showing BMI trajectories, given that this was a part of the primary analysis
R: Thank you for suggesting. We’ve added Figure 2 and Supplemental Figure 1 to show the trajectory.

8. There are several missing variables which should have been considered, such as feeding, gestational diabetes, maternal smoking, as well as prenatal and perinatal data.
R: This is a good suggestion. However, we could not follow these requirements because our research is a retrospective study.

9. Are the results for birth weight on table 5 correct?
R: We derived birthweight-for-gestational-age z-scores using references from International standards for newborn.(Reference 29) The results for birth weight have been changed.

10. Overall the discussion needs to be improved. The study findings need to be better commented. In addition, the authors should comment the clinical relevance of the small differences in age and magnitude of peak BMI between boys and girls. The statistical significance is related to the large sample size

R: Thank you for suggesting. We have now changed this as suggested. （page 12, line 22.）

11. Tables 1 and 2 are not necessary
R: This is a good suggestion. We have deleted these two tables.

Reviewer: 4
Reviewer Name: Jenny M Kindblom
Institution and Country: Institue of Medicine, University of Gothenburg, Sweden
Please state any competing interests: None declared

Please leave your comments for the authors below

This is a well-motivated study of the infancy BMI peak and its association with overweight/obesity at 2 years of age in a Chinese cohort. The authors present descriptive statistics of the BMI peak and the associations between the BMI peak and the increased risk of overweight and obesity at 2 years of age. Their main result is that higher and later BMI peak was associated with increased risk of overweight /obesity at age 2 years.

I have three major concerns about this study:
1. The inclusion process of the subjects needs to be clarified. As described in the Methods section, the cohort started off with 10,674 infants and ended up with 1,949 infants included in the study. This results in only 18% included subjects from the original population-based cohort and a high risk of selection bias. I suggest:
a. To clarify the inclusion criteria, with the removal of "also" line 27 page 4.
R: We apologize for this error and we have corrected it.

b. To include a figure of the inclusion process with n-numbers for the different exclusions steps, and the actual number of included subjects, to illustrate the inclusion process.
R: This is a good suggestion. We have added Figure 1.

c. To be consequent in the reporting of the percentage and n-numbers of included subjects (Abstract, Methods section, the second paragraph in the Discussion section, and Tables). There are different n-numbers in the abstract, the methods and the tables, which is confusing.
R: We apologize for this error and we have corrected it in the manuscript.

d. To address this possible selection bias in the discussion as a limitation of the study, and also the results of the association need to be toned down.
R：Thank you for this suggestion. To assess potential selection bias, we compared demographics and birth characteristics of the analytic sample(n=2268) to the excluded healthy singleton infants (n=4806). There were no substantial differences in sex, birth weight, maternal age or overweight and obese rates at age 2 years of the two samples.We have now changed this as suggested. (Supplemental Table 1)

2. The statistical analyses in the Methods section needs to be clarified. Define the variables (magnitude and timing of BMI peak, BMI peak, velocity to peak) and specify which covariates are included in table 5 so that this information is available in table 5
R: This is a good suggestion. We have changed it as follows.
BMI peak characteristics [age (in months) and magnitude (BMI; in kg/m2) at peak and pre-peak velocities] were estimated. Gender, delivery mode and maternal ages were defined as categorical variables. Birth weight, duration of breastfeeding and sleeping were defined as continuous variable.

3. I am also concerned that there might be a potential selection bias due to that there are more large-at-birth infants with inestimable peak BMI. Since infants with higher birth weight was inestimable to a higher extent than infants with low or normal birth weight, it might have implications of the results for the association analysis given that birth weight is associated with peak BMI and childhood overweight and obesity. I suggest to add an analysis of overweight and obesity under the title “General characteristics of children at age two years” page 8.
R: This is a good suggestion. We have caculated it as follows.
There was no difference between the two groups in sex, birth weight, maternal age, duration of breastfeeding, duration of sleep and overweight and obese rates (17.5% vs 11.9%, P=0.075) at age 2 years.

Minor comments:
1. Abstract/Objectives: Insert “populations” after European (line 12).
R: We apologize for this error and we have corrected it in the manuscript.

2. Abstract/Objectives: Add the second aim, to investigate the association between infant BMI peak and overweight/obesity at 2 years of age.
R: We apologize for this error and we have added it in the manuscript.

3. Abstract/Methods: Is n=2073 valid? See major comment 1.
R: Yes, it is valid. Subjects with estimable (n=2073) were established to estimate BMI growth curves. Subjects with inestimable (n=195) were excluded.

4. Abstract/Methods: Is there a difference between higher infant BMI peak and higher magnitude of infant BMI peak? Please specify.
R: Thank you for this suggestion and we havechanged it as suggested.
BMI peak characteristics [age (in months) and magnitude (BMI; in kg/m2) at peak and pre-peak velocities] were estimated. With the peak BMI value increasing by 1 kg/m2 or the peak time by 1 months every time, the risk of overweight at age 2 years increased by 2.11 times (OR 3.11; 95% CI 2.64-3.66) and 35% (OR 1.35; 95% CI 1.21-1.50) respectively.

5. Abstract overall: Insert “at age 2 years” after childhood overweight/obesity on at least one occasion.
R: We apologize for this error and we have added it in the manuscript.

6. Line 15, page 4. “…the missing of the subjects”, replace with “…loss to follow-up”.
R: Thank you for this suggestion and we have changed it in the manuscript.

7. Why was the interval 14-408 days chosen as to where the BMI peak should occur? Please provide a rationale.
R: We considered BMI data between 14 and 408d of age to allow for a time lag before the outcome ascertainment (at 2 y) and to avoid the period of neonatal weight loss seen in the first 2 week of life. There are two articles (Reference19,23) making 13.5m as a cut-off time. Some children's physical examination time may also be delayed for one months, so that more samples can be included in the study.

8. Table 2 should be removed and the information of the covariates should be added to the table text in Table 5. See major comment 2.
R: This is a good suggestion. We have deleted Table 2.

9. Table 5 table text, include which analyses that have been used.
R: We have added as suggested.

10. Table 5, the OR and 95% CI for birth weight are odd.
R: We derived birthweight-for-gestational-age z-scores using references from International standards for newborn. The results for birth weight have been changed. </vif

VERSION 2 – REVIEW

REVIEWER	Jianduan Zhang Huazhong University of Science and Technology, China
REVIEW RETURNED	24-Jun-2017

GENERAL COMMENTS	The authors discussed an interesting and important topic regarding the factors that might relate to early onset of overweight and obesity. The manuscript is well-written, however, the following concerns need to be addressed, mainly on the process of raw data collection and extraction for the analysis. It is perfectly fine to use a convenience dataset which I believe was what the authors did for the paper. However, rather than justifying the quality of the data, detailed descriptions of the overall process of data gathering in the field, the data extraction for analysis, and then thoroughly discuss the limitation of using this type of data would be of much value. The data used for the analysis was based on the raw data gathered from routine health checks of children, which were not designed specifically for scientific research purposes. This process involved numerous Health Care Centers and many healthcare providers. How confident would the authors be in the accuracy of the collected measurements, i.e., weight and length of the children? For instance, the weight could vary significantly with different clothing and this would heavily impact the BMI, which was used as the key outcome of the study. It would be helpful if the authors could present more details on how the data were collected to indicate the reliability of the results. The authors did not mention about how the data were obtained for the analysis. Was it obtained from the paper records, or extracted from the electronic systems? And if so, how? In page 30, line 15-16 the authors stated “Parents recalled to feeding and sleeping questions in follow-ups.” Were those questions part of the routine health checks in the study area? Did the authors mean in each follow-up? Were there any missing data on breastfeeding and sleeping durations? Page 7, line 43, “greater than 4 kg” shall be “equal to or greater than 4 kg”

REVIEWER	Izzuddin M Aris Singapore Institute for Clinical Sciences, A*STAR
REVIEW RETURNED	18-Jun-2017

GENERAL COMMENTS	The manuscript is improved, and have addressed the comments that have been put forward. Below are additional comments that can help to improve the clarity and brevity of the paper: 1) The authors acknowledge that there are better alternatives to the current statistical approach that was undertaken in the paper, and have partially addressed this issue in the Introduction (paragraph 4). The placement of this argument however, does not flow well with the statements in the mentioned introductory paragraph. The discussion

	regarding the utility of different modelling methods in deriving the BMI peak should be placed in the Discussion section, with a specific focus on how the current method used (i.e. conventional polynomial regression) fits with the aims and objectives of the paper 2) The authors reported that mean residual plots were used to describe the fit of the subject-specific curves. Please include these plots, as well as a description in the Methods. 3) For clarity to the readers, please elaborate the reasons in the Methods why the following subjects were excluded: preterm infants, term twins, post-term infants, and term infants with congenital defects 4) As the reliability of the anthropometric measurements cannot be ascertained due to the retrospective nature of the cohort, this should be addressed as a limitation of the study

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name
Izzuddin M Aris
Institution and Country
Singapore Institute for Clinical Sciences, A*STAR

The manuscript is improved, and have addressed the comments that have been put forward. Below are additional comments that can help to improve the clarity and brevity of the paper:

1) The authors acknowledge that there are better alternatives to the current statistical approach that was undertaken in the paper, and have partially addressed this issue in the Introduction (paragraph 4). The placement of this argument however, does not flow well with the statements in the mentioned introductory paragraph. The discussion regarding the utility of different modelling methods in deriving the BMI peak should be placed in the Discussion section, with a specific focus on how the current method used (i.e. conventional polynomial regression) fits with the aims and objectives of the paper

Response(R)： Thank you for this suggestion. We have now changed this content into the discussion section as suggested. (Page 39, Line 37-41)

2) The authors reported that mean residual plots were used to describe the fit of the subject-specific curves. Please include these plots, as well as a description in the Methods.
R: The residuals mentioned in this paper refer to Coefficient of determination (R2). We have added the suggested content into the methods section. (Page35, Line 5-8)

3) For clarity to the readers, please elaborate the reasons in the Methods why the following subjects were excluded: preterm infants, term twins, post-term infants, and term infants with congenital defects

R: We have now provided the justification for excluding these group of subjects, indicating that they may have different characteristics of curves compared to normal term children. This is also in tandem with the approach used in other populations, e.g. the USA study. The revised texts are found in page 32, line10-14.

4) As the reliability of the anthropometric measurements cannot be ascertained due to the

retrospective nature of the cohort, this should be addressed as a limitation of the study

R: We have changed this content into the discussion section as suggested. (Page38, Line51-55)

Reviewer: 1
Reviewer Name
Jianduan Zhang
Institution and Country
Huazhong University of Science and Technology, China

The authors discussed an interesting and important topic regarding the factors that might relate to early onset of overweight and obesity. The manuscript is well-written, however, the following concerns need to be addressed, mainly on the process of raw data collection and extraction for the analysis.

It is perfectly fine to use a convenience dataset which I believe was what the authors did for the paper. However, rather than justifying the quality of the data, detailed descriptions of the overall process of data gathering in the field, the data extraction for analysis, and then thoroughly discuss the limitation of using this type of data would be of much value.
The data used for the analysis was based on the raw data gathered from routine health checks of children, which were not designed specifically for scientific research purposes. This process involved numerous Health Care Centers and many healthcare providers. How confident would the authors be in the accuracy of the collected measurements, i.e., weight and length of the children? For instance, the weight could vary significantly with different clothing and this would heavily impact the BMI, which was used as the key outcome of the study. It would be helpful if the authors could present more details on how the data were collected to indicate the reliability of the results.
The authors did not mention about how the data were obtained for the analysis. Was it obtained from the paper records, or extracted from the electronic systems? And if so, how?

R: We have mentioned the records were extracted from the electronic systems. (Page 5, Line 58) The records system is administrated by Jing'an Maternal and Child Health Center. When the abnormal data was put into the system, the software will be in error to mention the doctor to revise it .The community surveyors were all trained by the center and methods of measurement were administrated every month for assessment and quality control. The records of measurement are further verified and compared with the previous records.

In page 30, line 15-16 the authors stated “Parents recalled to feeding and sleeping questions in follow-ups.” Were those questions part of the routine health checks in the study area? Did the authors mean in each follow-up? Were there any missing data on breastfeeding and sleeping durations?

R: Parents reported the data in each follow-up as part of the routine health chceks rather than a few years from the memories. The physical examination system requires complete data to be saved, so there were no missing data on breastfeeding and sleeping durations.

Page 7, line 43, “greater than 4 kg” shall be “equal to or greater than 4 kg”

R: Thank you for this suggestion. We have changed it as suggested.

We thank the reviewers who pointed out areas of our manuscript that needed corrections and improvement. We also thank you for the opportunity to resubmit a revised copy of our paper.

We hope that you will find the revised manuscript suitable for publication in BMJ Open.

VERSION 3 – REVIEW

REVIEWER	Jianduan Zhang Huazhong University of Science and Technology
REVIEW RETURNED	27-Jul-2017

GENERAL COMMENTS	In page 2, the authors' statement, "As we lacked data on parent's BMI and pregnancy weight gain, we could ascertain the influence of these on infant BMI peak and contribution to childhood overweight and obesity", does not sound logical to me. I think an important NOT might be missing in the sentence? In Page 11, the authors stated that "The data used in our analysis were routinely collected by the health centers where children are offered routine healthcare, such as immunizations and physical examination; thus, the collected measurements are a valid and reliable data set for addressing the study questions", which I found not convincing. The routine healthcare activity is not established for a scientific research purpose and it is still under debate whether such data could and to what degree be used to answer scientific questions. The data obtained from the day-to-day work, for example, the children' weight and length measured by health care staff at Community Health Center were neither performed under a strict protocol nor being vigorously monitored. The bias of such data could be large and its accuracy could be questionable. Therefore, the conclusion based on a study with its main and only outcome variable generated from routinely collected data, should be interpreted with extra cautious. The weakness and potential risks of using such data for research purpose should be fully addressed/acknowledged in the manuscript, to avoid delivering wrong messages to readers and resulting in an overestimation the value of using such data in research and overgeneralization of the conclusion.

VERSION 3 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 1
Reviewer Name: Jianduan Zhang
Institution and Country: Huazhong University of Science and Technology
Please state any competing interests: None declared.
Please leave your comments for the authors below
In page 2, the authors' statement, "As we lacked data on parent's BMI and pregnancy weight gain, we could ascertain the influence of these on infant BMI peak and contribution to childhood overweight and obesity", does not sound logical to me. I think an important NOT might be missing in the sentence?

R: Thank you for this suggestion. We have now added this word 'not' into the sentence as suggested. (Page29, Line17)

In Page 11, the authors stated that “The data used in our analysis were routinely collected by the health centers where children are offered routine healthcare, such as immunizations and physical examination; thus, the collected measurements are a valid and reliable data set for addressing the study questions”, which I found not convincing.
The routine healthcare activity is not established for a scientific research purpose and it is still under debate whether such data could and to what degree be used to answer scientific questions. The data obtained from the day-to-day work, for example, the children’ weight and length measured by health care staff at Community Health Center were neither performed under a strict protocol nor being vigorously monitored. The bias of such data could be large and its accuracy could be questionable. Therefore, the conclusion based on a study with its main and only outcome variable generated from routinely collected data, should be interpreted with extra cautious. The weakness and potential risks of using such data for research purpose should be fully addressed/acknowledged in the manuscript, to avoid delivering wrong messages to readers and resulting in an overestimation the value of using such data in research and overgeneralization of the conclusion.

R: Thank you for your suggestion. We have removed this sentence "The data used in our analysis were routinely collected by the health centers where children are offered routine healthcare, such as immunizations and physical examination; thus, the collected measurements are a valid and reliable data set for addressing the study questions". In the limitation section, we have acknowledged the potential risks of using such data for research purpose as following:
Additionally, the reliability of the anthropometric measurements could not be ascertained due to the retrospective nature of the cohort. We acknowledge that the generated from routinely collected data may potentially influence the generalizability of the findings. (Page38, Line45)
In the conclusion section, we also mentioned it as following:
Further studies from other urban populations in China are required in order to confirm or question our observations. (Page40, Line37)

VERSION 4 – REVIEW

REVIEWER	Jianduan Zhang Huazhong University of Science and Technology
REVIEW RETURNED	14-Aug-2017

GENERAL COMMENTS	No more comments.