PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of Low Birthweight with Thinness and Severe Obesity in 3 to 12-Year-Old Children: A large-scale population-based cross-sectional study in Shanghai, China.
AUTHORS	Chen, Chang; Jin, Zhijuan; Yang, You; Jiang, Fan; Huang, Hong; Liu, Shijian; Jin, Xingming

VERSION 1 - REVIEW

REVIEWER	Emilien Jeannot Institut of global Heath, Geneva, Switzerland
REVIEW RETURNED	11-Jan-2019

GENERAL COMMENTS	The study and article are interesting, although it does not bring much new in a field (relationship between birth weights and future obesity or thinless) evidence-based is contradictory and still not reliable. The study has some weaknesses and limitations principally the cross sectional desing, and also Methodology for the collection of data by self-declaration Follow my comments that may allow authors to improve their text for publication in the open BMJ. P2 , Line 22-23 : explained between which variables the Logistic regression must evaluate the association. background is well explained, including the current difficulty of knowing the sense of the relationship between the birth weight and the probability of a future obesity or thinness. Studies exploring this phenomenon often have a relatively weak study design: The effect found RR or OR are often weak and contradictory, making the causality and interpretation of the results of these studies very difficult to interpret and use. This study does not escape this problem despite its large sample size. Methods A sample size has been calculated to support your hypothesis? if yes, it is not included in the article or in reference 14? Measurement : It would be interesting to put the questionnaire given to the parent in Appendix

The fact that the questionnaire and the data collected are done by self-declaration is a very important bias, with a risk of under assessment or on assessment of the BMI very important, an mistake understanding of the questions and filling out the questionnaires is also a risk

Did the parents have help filling out these questionnaires? flyer instruction or something?
P4 Line 39 : For the Birthweight declaration, many parents know this data?
P5 line4-12: Are the parents reporting all these Neonatal variables? I find it incredible that so many parents know all this information and report it without bias.

Statistical analysis

P5 line 38-40. It should be explained the level of significance (p<0.05 or other) which selected univariate analysis variables were introduced into the multivariate model
Result

Line 14-25 and 30-38: IC95% must be indicated for each of these prevalence

Line 44-45 Table 2: Why in Model 1, multivariate analysis was adjusted only for gender and Age, this should be explained more in the statistical analysis section.

The choice of models 2 and 3 should also be better explained in the statistical analysis section.

P7 line 8: it is interesting to see that in model 3 the BW seems to be a protective factor for the overweight OR=0.87 CI95 0.76-0.99.
Discussion
P7 line 51: «possible Explanation was small sample size» how can you say that, because if you turned off your full sample size?

I don't think the results you find are related to the size of the sample that is large, other causes are to be investigated.
P9 line 18: Your design cross sectional is indeed an important limit, it is a weak design to try to determine the etiology of a health phenomenon as studied in this study. It does not allow for a strong conclusion with a high level of evidence based.
P9 line 22: Collected data by self-reported is a very important Bias, there is a major risk of false evaluation of real BMI'S children, a risk of misunderstandings of the questions on neonatal Outcome is also possible.
P9 line 26: "more Accurate…." exact is the only procedure to have a precise indication of the actual BMI of the children, although it is an indicator BMI is increasingly questioned for its relevance about the assessment of overweight and obesity in children.
P9 line 40: one of the aims of this study would be to prevent children from being born with a low birth weight, by creating an environment favourable to mothers during their pregnancy, with recommendation, on their consumption of alcohol, tobacco, physical activity ect...

REVIEWER	Ragnhild Falk
	Oslo University Hospital, Norway
REVIEW RETURNED	17-Jan-2019

GENERAL COMMENTS	It's a paper studying an interesting aim; the association between low birthweight and childhood weight. However, I am struggling with some of the numbers and the methods.
	In the description of the study design the author states that the children are 3-12 year old, while in table 1 the 12-year category is missing.
	The authors state that birthweight is divided into three groups, low, normal and high. The last category is not included in the results in table 1.
	In the results, second sentence, the study sample consists of 70284 children. While only 62715 is included in table 1. Further, I suggest that the number with missing information should be included as a separate category. E.g. Add that 2065 (6.3%) of the boys has missing info of one-child family, otherwise calculated the percentages of the total number.
	What kind of questionnaire was used? Please give the original reference.
	In the statistics section, the author state that multivariable logistic regression was performed. Whereas in the header of table 2 it is stated that results of multivariate logistic regression models were presented. Or is it actually multinomial logistic regression? Birthweight should be considered as the exposure variable and weight in childhood as the outcome, thus a multinomial logistic regression is well suited, since there are seven categories of the outcome. Is that what the authors have performed? The set-up of table 2 confuses me. Normally, the outcome categories are defined as columns and exposure as rows. The number of observations in the analyses should be clearly stated.
	Did the authors consider a multilevel analysis, e.g. using GEE method?
	In figure1, instead of a standard chi-square test, a trend test [called linear-by-linear test in SPSS] could be considered.
	Ethnicity could be a possible confounding factor. Do you have any information about origin of the children?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

The study and article are interesting, although it does not bring much new in a field (relationship between birth weights and future obesity or thinness) evidence-based is contradictory and still not reliable. The study has some weaknesses and limitations principally the cross sectional design, and also Methodology for the collection of data by self-declaration. Follow my comments that may allow authors to improve their text for publication in the open BMJ.

P2, Line 22-23: explained between which variables the Logistic regression must evaluate the association.

Response: We used logistic regression to estimate the association between birthweight and BMI category. We have added this part on Page 3 Line 25.

Background is well explained, including the current difficulty of knowing the sense of the relationship between the birth weight and the probability of a future obesity or thinness. Studies exploring this phenomenon often have a relatively weak study design: The effect found RR or OR are often weak and contradictory, making the causality and interpretation of the results of these studies very difficult to interpret and use. This study does not escape this problem despite its large sample size.

Response: Thanks for the reviewer's insightful judgment. Though we try to explore the relationship between birthweight and severe obesity based on the large sample size, we only detected weak effects of low birthweight on BMI category in our study, and the long-term health effects cannot be neglected. Post-natal care is still necessary and attention should be paid on its impact on children's growth and development.

Methods

A sample size has been calculated to support your hypothesis? if yes, it is not included in the article or in reference 14?

Response: We have added the reference 15 which described the sample size calculation in the method section and updated all the references. Our study was part of a population-based survey of autism spectrum disorder funded by the Shanghai Municipal Commission of Health and Family Planning: Shanghai Municipal Enhancing Public Health 3-year Program. The sample size was calculated according to the prevalence of autism spectrum disorder (11.8 per 10,000 children). As described in reference 15, 134f 949 (14.12%) kindergartens and seventy of 436 (16.06 %) elementary schools were sampled by multistage, stratified cluster random method, and 84,075 of totally 576,621 (14.58 %) shanghai children were recruited, which ensured the power of our analysis.

Measurement :

It would be interesting to put the questionnaire given to the parent in Appendix.

Response: The questionnaire was provided for review (Chinese version), we have emailed to the editor .

The fact that the questionnaire and the data collected are done by self-declaration is a very important bias, with a risk of under assessment or on assessment of the BMI very important, an mistake understanding of the questions and filling out the questionnaires is also a risk. Did the parents have help filling out these questionnaires? flyer instruction or something?

Response: We agree with the reviewer's comment that bias is unavoidable in self-reported questionnaires to some extent. However, we tried our best to minimize the risk and standardize the research process in the survey. Teachers participating in the survey underwent training so that they could give detailed instructions for filling, distribution and collection of the questionnaires to reduce bias in the study. Trained teachers distributed questionnaires to students, asked students to take the questionnaire home and students' parents filled in the questionnaire. The teachers collected the completed questionnaires and then returned them to the investigator. The information sheet for informing parents about the investigation was attached with the questionnaire. The details of the quality control process during the survey were described in reference 14 and 15.

P4 Line 39: For the Birthweight declaration, many parents know this data?

Response: Of 81,384 completed questionnaires, the information on weight/height and BW was available for 72,349 and 70,284 children respectively. In China most of the parents can clearly

remember their children's birthweight because the Chinese parents were very concerned about the BW due to one-child policy.

P5 line4-12: Are the parents reporting all these Neonatal variables? I find it incredible that so many parents know all this information and report it without bias.

Response: Many Chinese parents remember gestational age at delivery and caesarean delivery as well as their children's birthweight on the basis of one-child policy. Also, perinatal health card and free post-natal follow-up services enhance these memories.

Statistical analysis

P5 line 38-40. It should be explained the level of significance (p<0.05 or other) which selected univariate analysis variables were introduced into the multivariate model.

Response: As suggested, we have revised the Statistical analysis part on Page 6 Lines 44-53.

Result

Line 14-25 and 30-38: IC95% must be indicated for each of these prevalence

Response: We have added these in the results section on Page 7 Lines 30-44, 50-58, Page 8 Lines 2-3.

Line 44-45 Table 2: Why in Model 1, multivariate analysis was adjusted only for gender and Age, this should be explained more in the statistical analysis section.

The choice of models 2 and 3 should also be better explained in the statistical analysis section.

Response: We have added the explanation in the Statistical analysis section on Page 6 Lines 44-53 as the following: Model 1 adjusted for the basic characteristics, age and gender, which were all possible confounding factors of BMI category. Also, neonatal characteristics were reported to be associated with both birthweight and BMI category, and were further adjusted as a confounder in model 2. Socioeconomic characteristics could reflect the environmental and nutritional status to some extent and were finally adjusted in model 3. All confounding variables were entered into the multivariate regression model.

P7 line 8: it is interesting to see that in model 3 the BW seems to be a protective factor for the overweight OR=0.87 CI95 0.76-0.99.

Response: Since the upper 95% CI is near the marginal value 1.00 and it's upper 95% CI included 1.00 in model 2 and 3, we are cautious about this result.

Discussion

P7 line 51: <possible Explanation was small sample size>how can you say that, because if you turned off your full sample size? I don't think the results you find are related to the size of the sample that is large, other causes are to be investigated.

Response: Accordingly, we reviewed the literature and updated the reference list on Page 9 Lines 15-27. And the corresponding discussion was revised as the following: Another possible explanation might be that the potential of growth has not been fully developed among those low birthweight children. Not all low birthweight children undergo catch-up growth, and different growth patterns might exist. Special attention should be paid to those low birthweight children in future cohort study.

P9 line 18: Your design cross sectional is indeed an important limit, it is a weak design to try to determine the etiology of a health phenomenon as studied in this study. It does not allow for a strong conclusion with a high level of evidence based.

Response: We agree with the reviewer's view. Our study only provides etiological clues for the relationship between birthweight and BMI, and we call for further cohort studies to explore and track growth trajectory of low birthweight children.

P9 line 22: Collected data by self-reported is a very important Bias, there is a major risk of false evaluation of real BMI'S children, a risk of misunderstandings of the questions on neonatal Outcome is also possible.

Response: Considering the practicability, it was very difficult to measure weight and height in such a large-scale population study, and we have emphasized these limitations again in the discussion section on Page 3 Lines 55-57 and Page 10 Lines 49-53.

P9 line 26: "more Accurate…." exact is the only procedure to have a precise indication of the actual BMI of the children, although it is an indicator BMI is increasingly questioned for its relevance about the assessment of overweight and obesity in children.

Response: We have revised this on Page 10, Line 59 and Page 11 Lines 8-12 as the following: Our results suggest a need for carefully designed longitudinal cohort studies with precise physical examination and indicators to document thinness and obesity among low birthweight children.

P9 line 40: one of the aims of this study would be to prevent children from being born with a low birth weight, by creating an environment favourable to mothers during their pregnancy, with recommendation, on their consumption of alcohol, tobacco, physical activity ect...

Response: Accordingly we have added this public health significance on Page 11 Lines 15-19.

Reviewer: 2

It's a paper studying an interesting aim; the association between low birthweight and childhood weight. However, I am struggling with some of the numbers and the methods.

In the description of the study design the author states that the children are 3-12 year old, while in table 1 the 12-year category is missing.

 Response: In table 1, 11 means 11.0 - 12.0, 12-year is the upper limit in the current study, we have added "-" in table 1. Accordingly, we have used 3-12 year old in our previous studies in references 14 and 15, so we didn't change the age range.

The authors state that birthweight is divided into three groups, low, normal and high. The last category is not included in the results in table 1.

Response: Totally 70,284 children provided complete data regarding weight, height, and birthweight. Among that, 3,359 children were born with low birthweight, 59,356 with normal birthweight, and 7,569 with high birthweight (Note: Shanghai is the most developed region in China). Because we only focused on low birthweight, children with high birthweight were excluded from our analysis

In the results, second sentence, the study sample consists of 70284 children. While only 62715 is included in table 1. Further, I suggest that the number with missing information should be included as a separate category. E.g. Add that 2065 (6.3%) of the boys has missing info of one-child family, otherwise calculated the percentages of the total number.

Response: As mentioned above, 7,569 with high birthweight were excluded, and there were 62,715 children remained in our final analysis. Also, we have added the missing category and recalculated the percentages in table 1.

What kind of questionnaire was used? Please give the original reference.

Response: The questionnaire of family social environment and growth development was a self-reported questionnaire, it was not a standard questionnaire, we have emailed it to the editor for review (Chinese version).

In the statistics section, the author state that multivariable logistic regression was performed. Whereas in the header of table 2 it is stated that results of multivariate logistic regression models were presented. Or is it actually multinomial logistic regression? Birthweight should be considered as the exposure variable and weight in childhood as the outcome, thus a multinomial logistic regression is well suited, since there are seven categories of the outcome. Is that what the authors have performed? The set-up of table 2 confuses me. Normally, the outcome categories are defined as columns and exposure as rows. The number of observations in the analyses should be clearly stated.

Response: Actually, multinomial logistic regression was performed and we have revised in the statistic analysis section on Page 6 Line 40, as reviewer mentioned, there were seven categories of the outcome, we have transposed the rows and columns in table 2 according to the reviewer's comment and we added the number of observations in the analysis.

Did the authors consider a multilevel analysis, e.g. using GEE method?

Response: Thanks for the reviewer's instructive comment. In our mind, GEE method fits repeated measurement longitudinal data, we will try multilevel analysis in our future study. And our cross-sectional design is indeed an important limit for the multilevel analysis.

In figure1, instead of a standard chi-square test, a trend test called linear-by-linear test in SPSS could be considered.

Response: We have performed Linear-by-Linear test, the Chi-Square value was 36.98 and P<0.001, and the results were added on Page 7 Line 28.

Ethnicity could be a possible confounding factor. Do you have any information about origin of the children?

Response: We don't have the ethnicity information but searched the website of Shanghai Ethnic and Religions (http://www.shmzw.gov.cn/mzw/index.html). There were 421,700 people with ethnic minorities background, accounted for 1.7% of 24.26 million Shanghai population. Since the proportion was small, the influence of ethnicity was likely to be diminutive on our results.

VERSION 2 – REVIEW

REVIEWER	Dr Emilien Jeannot Institute of Global Health, Geneva, Switzerland
REVIEW RETURNED	21-Mar-2019

GENERAL COMMENTS	The authors have upgraded their article and responded to our comments.

	I will have one last comment / addition to make.
	Abstract: add after the phrase " but did not correlate with overweight " OR of overweight with its confidence interval Results section: in the last paragraph describing table 2. I will add in the text the non-significant OR related to obesity and overweight as they are indicated in the Abstract

REVIEWER	Ragnhild Falk Oslo University Hospital
REVIEW RETURNED	15-Mar-2019

GENERAL COMMENTS	Thanks for the opportunity to review the revised version of the manuscript. Most of the issues that were raised have been answered. However, some further points need clarification. The linear-by-linear test should be described in the statistics section. And in the results section it is not clear which groups that is compared in "Linear-by-linear … (P<0.001)". Please clarify. The description of the regression analyses should be consistently described throughout the manuscript as multinomial logistic regression. Comparison of groups that is not statistically significant should not be described as different. E.g. in boys, the percentage of overweight and obesity were NOT lower in low vs normal BW, and should be stated as there were no difference between the groups. Please revise. Correlation should not be confused with association. The authors have performed regression analysis, thus association are being studied. Correlation analysis is something different. Please, rephrase all the sentences that describe results from the regression analyses.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

The linear-by-linear test should be described in the statistics section. And in the results section it is not clear which groups that is compared in "Linear-by-linear … (P<0.001)". Please clarify.

Response: Thanks for the reviewer's comment. We have added this part in statistics section as "The linear-by-linear trend test were performed to detect the distribution of different BMI categories between low and normal BW" on Page 5 Lines 22-24, and results section as "The distribution of different BMI categories between low and normal BW was examined by linear-by-linear trend test and the chi-square tests value was 36.98 (P<0.001) "on Page 6 Line 23.

The description of the regression analyses should be consistently described throughout the manuscript as multinomial logistic regression.

Response: Thanks for the reviewer's careful work and we have revised throughout the manuscript.

Comparison of groups that is not statistically significant should not be described as different. E.g. in boys, the percentage of overweight and obesity were NOT lower in low vs normal BW, and should be stated as there were no difference between the groups. Please revise.

Response: We have revised according to the reviewer's comment on Page 6 Lines 37, 51-54, 58-60.

Correlation should not be confused with association. The authors have performed regression analysis, thus association are being studied. Correlation analysis is something different. Please, rephrase all the sentences that describe results from the regression analyses.

Response: We are grateful to the reviewer's kind reminder. We have replaced "correlate" with "associate" and "correlation" with "association" throughout the manuscript.

Reviewer: 2

Abstract: add after the phrase " but did not correlate with overweight " OR of overweight with its confidence interval

Response: Thanks for the reviewer's comment. We have added these in the abstract on Page 2 Line 31-33.

Results section: in the last paragraph describing table 2. I will add in the text the non-significant OR related to obesity and overweight as they are indicated in the Abstract

Response: Thanks for the reviewer's comment and accordingly we have added the non-significant OR in the result section on Page 7 Lines 13-17, 27-29.