PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of the great east Japan earthquake on the body mass index of preschool children: a nationwide nursery school survey
AUTHORS	Yokomichi, Hiroshi; Zheng, Wei; Matsubara, Hiroko; Ishikuro, Mami; Kikuya, Masahiro; Isojima, Tsuyoshi; Yokoya, Susumu; Tanaka, Toshiaki; Kato, Noriko; Chida, Shoichi; Ono, Atsushi; Hosoya, Mitsuaki; Tanaka, Soichiro; Kuriyama, Shinichi; Kure, Shigeo; Yamagata, Zentaro

VERSION 1 - REVIEW

REVIEWER	Anahit Demirchyan, MD, MPH School of Public Health, American University of Armenia
REVIEW RETURNED	20-Jan-2016

GENERAL COMMENTS	The abstract does not include information on the ecological study comparing proportions of overweight school-age children across the study areas. This should be added. The study used child growth patterns in three unaffected prefectures as reference against which the growth patterns of children in the affected areas were compared, while in reality these patterns could be different regardless of the earthquake. To address this concern, I would recommend, in addition to evaluating the BMI changes after the earthquake starting from the reference baseline time point of October 2010, evaluate also the BMI changes before the earthquake against another baseline time point of April 2008, as data is available starting from April 2008. Although the growth patterns before the earthquake are reflected in the figures, they are not compared statistically, while demonstrating that the growth patterns in the compared areas were statistically not different before the earthquake would add to the validity of the study. If there is available data, a better approach to address the research question could presumably be to apply different strategy of the study and instead of comparing growth patterns of children in affected and unaffected areas, to compare growth patterns of two subsequent cohorts of children in each of the affected areas, with the first (earlier) cohort passing the studied age points before the earthquake and the second – after experiencing the earthquake. A serious limitation of the study is omitting those children who were not able to attend nursery schools after the earthquake. Probably, these children suffered more from the consequences of the earthquake, as they were most likely injured/relocated and experienced more diet/lifestyle changes because of these. Thus, basing the analysis on the assumption of missing at random seems unjustified. The study does not provide the proportions of those children (in each area) not included in the analysis because of stopping to attend nursery schools after the earthquake. Providing these

	proportions would help to estimate the degree of the bias this limitation could cause. While the analysis was controlled for children's age and gender, no other factors (family, dietary, lifestyle, etc.) were controlled for during the analysis, and this could possibly influence the results of the study. Although many of the study limitations are discussed in the paper, the size of possible bias these limitation could cause is not estimated. The issue whether those children included in the study were representative for the same-age population in the affected areas is open. Authors use a term NPR (nursery school participation rate) that is not explained in the paper. Is this the proportion of children in the given area who attend nursery schools? If it is, efforts should be made to compare the characteristics of those children who attend nursery schools and those who do not attend those schools to demonstrate whether one group could be representative for the other. Otherwise, the study results should be applied only to students of nursery schools and not children in general. Also, it is not clear – the provided NPRs reflect the situation before the earthquake or after?

REVIEWER	Shin Amemiya Department of Pediatrics, Saitama Medical University, Japan
REVIEW RETURNED	25-Jan-2016

GENERAL COMMENTS	To Editor This paper is important because of consideration of the impact of grave disaster on toddlers' metabolic disturbances due to environmental changes thereafter. The authors considered that environmental changes for a few years following a grave disaster would not only result in weight-gain or obesity in toddlers but also metabolic disorders later in their future. Since toddlers were during the period of adiposity rebound, they might suffer from metabolic disarrangement in their future due to epigenetic effect or something else. The authors proposed the urgent healthy environment preventing obesity and so forth, and the need for follow-ups to care for future metabolic changes. The authors also clarified the different influences on health problems between earthquake, tsunami and nuclear accident in Fukushima and those without nuclear accident in Miyagi and Iwate, compared to unaffected prefectures in north Japan and across Japan. I would like to suggest the authors to use BMI percentile data for age and sex in Japanese 2000 data for the international definition of overweight and obesity. To Authors General comments: This paper is interesting because of comparison of BMI changes in toddlers resided in between affected and unaffected prefectures. Although the follow-up data in those toddlers were limited to a few years after the great east earthquake, the authors chose the subjects focusing on toddlers during the period of adiposity rebound which might affect metabolic disorders in their later life. Regretfully, the authors did not use BMI percentile to determine the international definition of overweight and obesity, since the Japanese BMI percentile for age and sex may be available, in addition to or instead of obesity index for age and sex in Japanese.

REVIEWER	Tetsuro Kobayashi Okinaka Memorial Institute for Medical Research, Japan
REVIEW RETURNED	03-Feb-2016

GENERAL COMMENTS	The manuscript by Yokomichi et al. is well documented report on the effects of big earthquake on BMI. I have a few comments. 1. Statistical analysis: What kind of analysis was done? How about multiple comparison results in 3 affected areas? 2. Study participants selection Selection criteria and exclusion criteria is not clearly documented. Inclusion criteria of “only those who did not relocate” is unclear. How about the recruitment rate of each study area. 3. Presentation of BMI change in each cohort area situation for foods intake and physical activity would be strikingly different between the evacuees because of tsunami and proper habitants of the affected areas. It will be helpful to plot the sampling points and affected area by tsunami on Fig.1. Addition of the data on the proportion of the evacuees in 3 study areas will be helpful because the effects of tsunami and /or those of nuclear power plants accidents in the areas are potentially different .

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewers

As requested, we have prepared a revised version of our manuscript and hope that we have addressed the concerns of reviewers #1–3. Our point-by-point responses to the reviewer comments are as follows: the reviewer comments are in italics, and our responses are designated according to line numbers in the revised manuscript. Please extend our sincere thanks to the reviewers for all of their helpful comments.

Responses to Reviewer #1

1. *The abstract does not include information on the ecological study comparing proportions of overweight school-age children across the study areas. This should be added.*

We appreciate your helpful suggestion for improving the manuscript. We have added the methodologies and results of the ecological study to the Abstract section.

Line 44: The ecological study examined random samples of school children from the affected prefectures.

Line 47: The ecological study evaluated post-disaster changes in the prevalence of overweight children.

Line 58: The ecological study detected increases in the prevalence of overweight boys and girls in Fukushima who were 6–11 and 6–10 years of age, respectively.

2. *The study used child growth patterns in three unaffected prefectures as reference against which the growth patterns of children in the affected areas were compared, while in reality these patterns could be different regardless of the earthquake. To address this concern, I would recommend, in addition to evaluating the BMI changes after the earthquake starting from the reference baseline time point of October 2010, evaluate also the BMI changes before the earthquake against another baseline time point of April 2008, as data is available starting from April 2008. Although the growth patterns before the earthquake are reflected in the figures, they are not compared statistically, while demonstrating that the growth patterns in the compared areas were not statistically different before the earthquake would add to the validity of the study.*

Thank you very much for your suggestions for strengthening the validity of our study. We selected October 2010 as the reference date because in contrast to that of adults whose heights and weights are relatively stable, difference-in-difference analysis is difficult for assessing BMIs of growing children. We did not perform a statistical analysis of the difference of BMIs between affected and unaffected children at each time point, because the focus of this study was to conduct difference-in-difference tests to compare BMI changes from the baseline between affected and unaffected children. We revised the manuscript accordingly as follows:

Line 131: Because of the difficulty in comparing BMIs of growing children between different areas, the BMI changes after the earthquake were evaluated from a reference baseline time point of October 2010, the last measured time point prior to the date of the earthquake (11 March 2011), through April 2011, October 2011, April 2012 and October 2012. We compared the BMI changes of children in each affected prefecture with those in the unaffected prefectures using a repeated-measures ANOVA model for mean changes from baseline[16] (diff BMI) for a difference-in-difference analysis of longitudinal data.[15]

3. *If there is available data, a better approach to address the research question could presumably be to apply different strategy of the study and instead of comparing growth patterns of children in affected and unaffected areas, to compare growth patterns of two subsequent cohorts of children in each of the affected areas, with the first (earlier) cohort passing the studied age points before the earthquake and the second–after experiencing the earthquake.*

Thank you very much for your suggestion of a new approach to strengthen the results. Because earlier cohort data in the prefectures are unavailable for the present study, we were limited to the design.

4. *A serious limitation of the study is omitting those children who were not able to attend nursery*

schools after the earthquake. Probably, these children suffered more from the consequences of the earthquake, as they were most likely injured/relocated and experienced more diet/lifestyle changes because of these. Thus, basing the analysis on the assumption of missing at random seems unjustified.

Thank you very much for your insightful comments about the serious limitation imposed by the bias caused by missing data after enrolment of the cohort. We agree that the restricted data represent a significant limitation. Because data were unavailable for those who did not attend nursery schools, we performed a complete case analysis in the present study. We have deleted 'missing at random' to clarify the details of missing data that we meant. In the revised manuscript, we have included the description of the primary limitation, referred to the potential bias imposed by the restricted data, and discussed their interpretations accordingly.

Line 70:

- The cohort of affected participants did not include those who died or relocated.

Line 112: The study participants were children who attended nursery schools that responded to the letter of request. Missing data included that for children who did not attend the participating nursery schools, moved out of the prefectures or died.

Line 359: The primary limitation was the representativeness of the sample populations in affected prefectures of northeast Japan. The registered children with available data attended nursery schools that responded to the letter of request. Therefore, the data did not include children who died; those in destroyed nursery schools, nursery schools without schoolteachers or other deficiencies or those who had moved away from the area. Because data were not available indicating whether the most severely affected children gained or lost weight, the direction and the amount of this bias in BMI were not determined. Conversely, the study design could have specifically focused on children who experienced severe suffering. Because of the study design, the definition of 'affected' children did not identify those who were evacuated to provisional houses or who were physically impacted by the tsunami. Therefore, the observed influence of the disaster on their child growth may have been diminished, and the data may not reflect all children in the affected prefectures. However, if the bias should exist, the effects of the earthquake on BMIs would be attenuated according to the observed data and bias toward the null hypothesis. Thus, we consider that the conclusions from the attenuated results would be held.

5. *The study does not provide the proportions of those children (in each area) not included in the analysis because of stopping to attend nursery schools after the earthquake. Providing these proportions would help to estimate the degree of the bias this limitation could cause.*

Thank you for your suggestion to help interpret the results. We confirm that the data analysed were

collected through April 2008 to October 2012 and that there are no longitudinal missing values. We have described the proportions of participants among the resident children.

Line 115: Because there are no published data of year 2011 for the exact number of the children born in fiscal year 2006 in each prefecture, the approximate proportion of participants among the resident children was calculated according to the number of the first grade primary school students in fiscal year 2012.[13]

Line 193: The data for the affected children on approximately 8.8% of resident children were collected from 646 boys and 597 girls who attended 97 nursery schools in Fukushima, 904 boys and 854 girls from 132 nursery schools in Miyagi and 483 boys and 458 girls from 81 nursery schools in Iwate. The data for the unaffected children on approximately 12.3% of resident children were collected from 307 boys and 285 girls attending 42 nursery schools in Yamagata, 762 boys and 739 girls from 88 nursery schools in Akita and 638 boys and 634 girls from 108 nursery schools in Aomori.

6. *While the analysis was controlled for children's age and gender, no other factors (family, dietary, lifestyle, etc.) were controlled for during the analysis, and this could possibly influence the results of the study. Although many of the study limitations are discussed in the paper, the size of possible bias these limitation could cause is not estimated.*

We appreciate this point-out for the amount of the bias originated from familial and cultural factors. Because we could not find published data describing the difference in baseline BMIs between growing children residing on either the Pacific Ocean or the other side of northeast Japan, we were unable to estimate the size of the possible bias. We have included the details of this limitation.

Line 71:

- The information on previous diets and physical activities was lacking.

Line 378: Second, the lack of information on diet and physical activity may limit the comparability of outcomes between the affected and unaffected prefectures studied. Because the Pacific Ocean side of northeast Japan receives less snow than the opposite side, exercise may be more frequent in the affected prefectures than in the unaffected prefectures. This cultural factor may induce bias toward decreasing BMIs of the affected children residing on the Pacific Ocean side. Considering this negative bias in BMI, the weight gains among children living in Fukushima and Iwate might be larger, and the weight loss observed in Miyagi might be smaller than thought. Because there is no published data for the difference in BMI between growing children residing on the Pacific Ocean side or the other side of northeast Japan, the amount of this potential bias was undetermined. To correct for this potential bias,

study initiation with a matching method based on cultural confounders for a quasi-experimental design might have reduced the bias. Even so, we minimised the bias by selecting an unaffected reference group from the northeast Japan, where the diet was considered to be similar to that in the three affected prefectures.[50]

7. *The issue whether those children included in the study were representative for the same-age population in the affected areas is open. Authors use a term NPR (nursery school participation rate) that is not explained in the paper. Is this the proportion of children in the given area who attend nursery schools? If it is, efforts should be made to compare the characteristics of those children who attend nursery schools and those who do not attend those schools to demonstrate whether one group could be representative for the other. Otherwise, the study results should be applied only to students of nursery schools and not children in general. Also, it is not clear–the provided NPRs reflect the situation before the earthquake or after?*

Thank you for your helpful suggestion for clarifying the proportions of participants among resident children and the investigation of their representativeness of the areas. NPR indicated the number of participating nurseries divided by the number of nursery schools. Instead, we have described the proportion of participants among the resident children. We were unable to find comparable published data on the characteristics and mean BMIs of preschool children according to prefectures. The data are potentially biased because nursery schools in Japan require that both parents must be employed, and children with stay-at-home mothers tend to attend kindergartens. This limitation has been included in the revised manuscript.

- Line 69: The study data were limited to nursery school records.

Line 115: Because there are no published data of year 2011 for the exact number of the children born in fiscal year 2006 in each prefecture, the approximate proportion of participants among the resident children was calculated according to the number of the first grade primary school students in fiscal year 2012.[13]

Line 193: The data for the affected children on approximately 8.8% of resident children were collected from 646 boys and 597 girls who attended 97 nursery schools in Fukushima, 904 boys and 854 girls from 132 nursery schools in Miyagi and 483 boys and 458 girls from 81 nursery schools in Iwate. The data for the unaffected children on approximately 12.3% of resident children were collected from 307 boys and 285 girls attending 42 nursery schools in Yamagata, 762 boys and 739 girls from 88 nursery schools in Akita and 638 boys and 634 girls from 108 nursery schools in Aomori.

Line 373: Additionally, because nursery schools in Japan require that either both parents or a single

parent without spouse should be employed, nursery school students may not represent the socio-economic status of all children in the studied prefectures. Therefore, although the comparisons of nursery school students in northeast Japan can be internally valid, it may not be possible to generalise the results to all preschool children who will be affected by another disaster.

Answers to the comments of reviewer #2

8. *I would like to suggest the authors to use BMI percentile data for age and sex in Japanese 2000 data for the international definition of overweight and obesity. Regretfully, the authors did not use BMI percentile to determine the international definition of overweight and obesity, since the Japanese BMI percentile for age and sex may be available, in addition to or instead of obesity index for age and sex in Japanese.*

We appreciate your insightful suggestion for utilising our data and illustrating the prevalence of overweight and obese children between the affected and unaffected prefectures before and after the earthquake. Although we considered the diagnostic criteria for overweight and obese Japanese children according to the data of the 2000 national growth survey of preschool children, there are no published cut-off values specific for sex and age-in-month for the 85th and 95th percentiles of the BMIs of Japanese children. Furthermore, we were unable to find published data for the 87th and 89th percentiles of BMI that correspond to 25 kg/m^2 BMI for the boys and girls aged 17.5 years, respectively. Therefore, for diagnoses of overweight and obese, we applied the criteria of the World Health Organization. We hope that this application will reveal the changes in prevalence of overweight and obese children before and after the earthquake.

Line 46:
Primary and secondary outcome measures: The cohort study compared post-disaster changes in BMIs and the prevalence of overweight and obese children.

Line 55: One month after the earthquake, Fukushima, Miyagi and Iwate had slightly increased prevalence of overweight boys, whereas Fukushima had slightly decreased prevalence of overweight girls, compared with the unaffected prefectures.

Line 92: Furthermore, this report compared the prevalence of overweight and obese children between affected and unaffected areas in a cohort and an ecological designs.

Line 161: For the secondary comparisons, the prevalence of overweight and obese children was compared between the affected and unaffected prefectures from October 2010 to 2011. Overweight and obesity were diagnosed according to the child growth standards of the World Health

Organization.[17] Because these diagnostic standards essentially change when children reach the age of 61 months, these secondary outcome comparisons were restricted to the data until October 2011 when almost half of the children were 60 months of age or younger. Although the difference in the changes in prevalence (i.e. proportions) between affected and unaffected prefectures is of interest, there is no published statistical test for such difference-in-difference analysis in proportional data. Instead, we applied Fisher's exact test to evaluate the difference in the prevalence of overweight and obese children between affected and unaffected prefectures, which were stratified according to date.

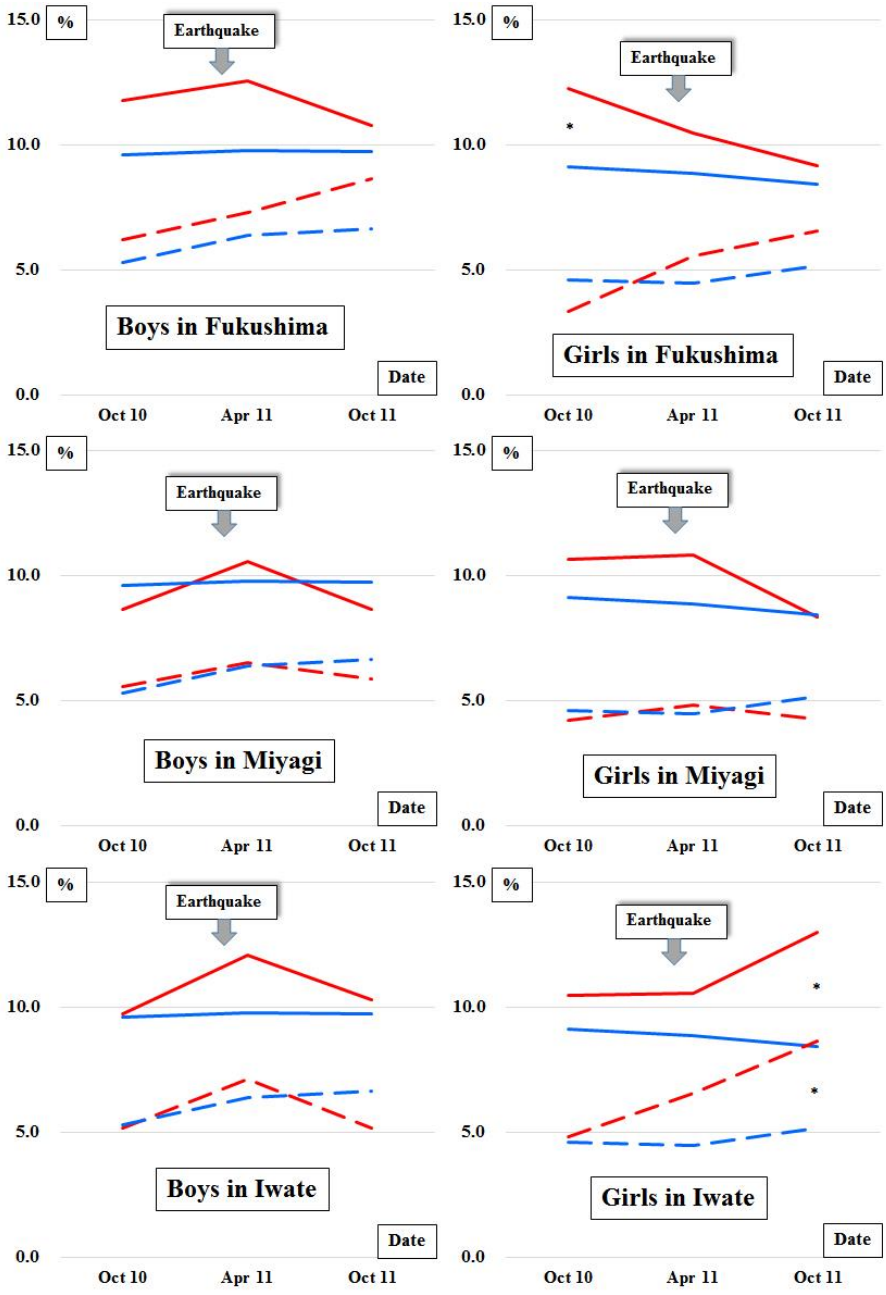
Line 230:

Comparison of the prevalence of overweight and obese children

Figure 4 shows the secondary comparisons of the prevalence of overweight and obese children in Fukushima, Miyagi and Iwate prefectures with the pooled population of the unaffected prefectures. Compared with the unaffected prefectures, there was a slight increase in the changes of the prevalence of overweight boys between October 2010 and April 2011 residing in Fukushima, Miyagi and Iwate. In contrast, there was a slight decrease in the change of the prevalence of overweight girls residing in Fukushima. Compared with the unaffected prefectures, a slight increase in the changes of the prevalence of obese individuals between October 2010 and April 2011 was observed among boys in Iwate and among girls in Fukushima, Miyagi and Iwate. In contrast, a slight decrease in the change of the prevalence of obese boys was observed in Miyagi.

Line 261: The prevalence of obese individuals in the cohort data increased to one month after the earthquake among boys in Iwate and among girls in the three affected prefectures, compared with that in the unaffected prefectures (Figure 4).

Figure 4 Prevalence of overweight and obese children in Fukushima, Miyagi and Iwate prefectures (red lines) and the unaffected prefectures (blue lines). Solid and dashed lines represent the prevalence of overweight and obese children, respectively. Overweight and obese were diagnosed according to the child growth standards of the World Health Organization.[17] * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$.



Answers to the comments of reviewer #3

9. *Statistical analysis: What kind of analysis was done?*

Thank you very much for your suggestion for improving our manuscript. We evaluated the mean changes from baseline, using a repeated-measures ANOVA model. We have specified the used model for the primary comparisons for Figure 3 and Table 2. Accordingly, we have changed the cited reference.

Line 135: We compared the BMI changes of children in each affected prefecture with those in the unaffected prefectures using a repeated-measures ANOVA model for mean changes from

baseline[16] (diff BMI) for a difference-in-difference analysis of longitudinal data.[15]

Line 139: The following fixed-effects model was employed:

$diff\ BMI_{ijk}$ = $(\text{Time point})_i$ + $(\text{Time point*Area group})_{ij}$ + $(\text{Age in month})_k$ + ε_{ijk}

References, Page 26:

16. Deiss D, Bolinder J, Riveline J-P, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care* 2006;29:2730–2.

10. *How about multiple comparison results in 3 affected areas?*

We appreciate your insightful comment about a multiple comparison that may affect interpretation of the manuscript. We considered that the effects of the earthquake on the changes in BMI in all of the three affected prefecture were of interest. We have revised the manuscript to clarify this study question.

Line 90: The present study was driven by the question of whether the body mass indices (BMIs) of the children in each affected prefecture had changed relative to the BMIs of comparable but unaffected children.

11. *Study participants selection*
Selection criteria and exclusion criteria is not clearly documented. Inclusion criteria of "only those who did not relocate" is unclear. How about the recruitment rate of each study area.

Thank you very much for the suggestion for improving the manuscript. We have modified the descriptions accordingly as follows:

Line 112: The study participants were children who attended nursery schools that responded to the letter of request. Missing data included that for children who did not attend the participating nursery schools, moved out of the prefectures or died. Because there are no published data of year 2011 for the exact number of the children born in fiscal year 2006 in each prefecture, the approximate proportion of participants among the resident children was calculated according to the number of the first grade primary school students in fiscal year 2012.[13]

Line 192:

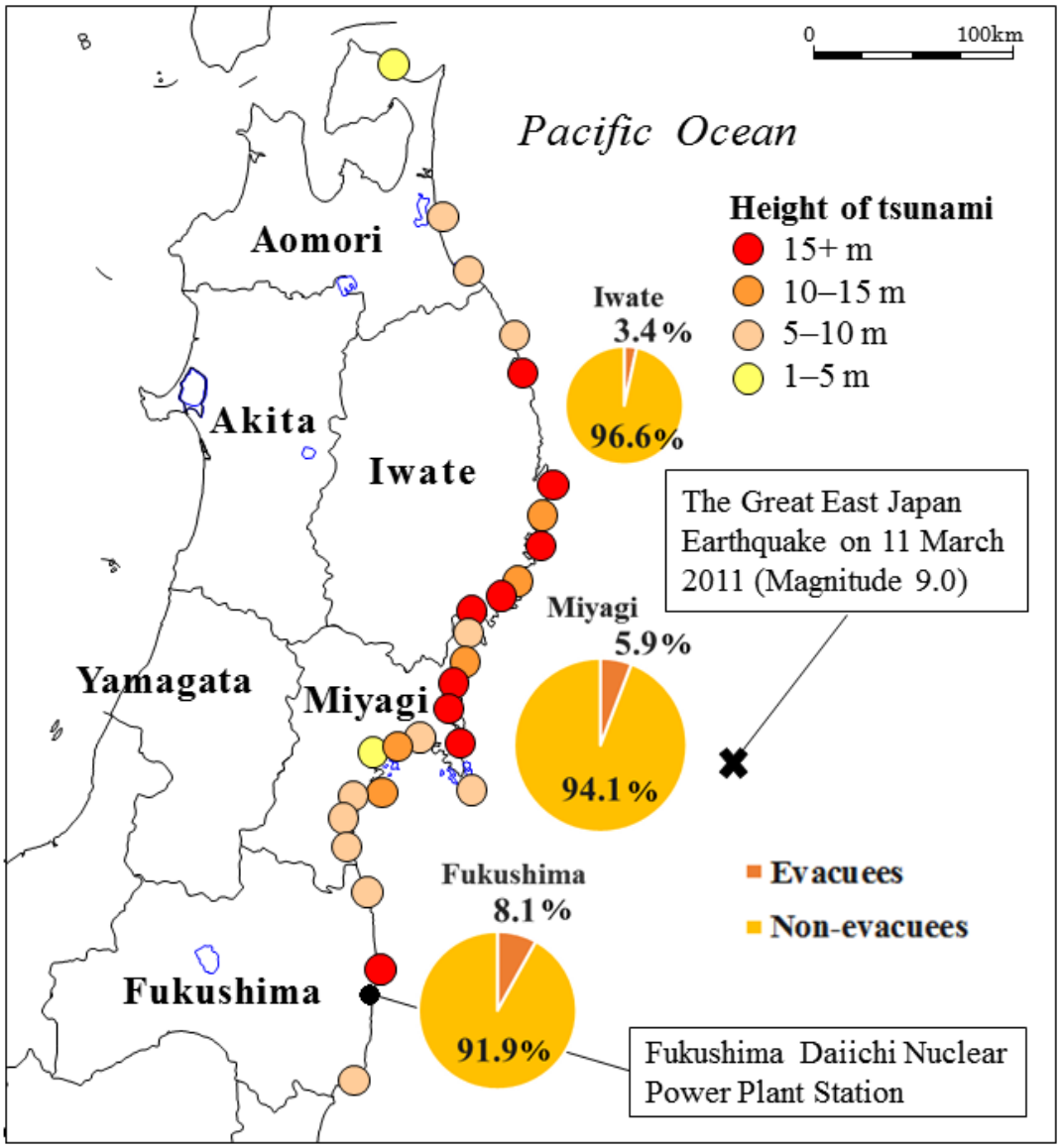
Comparison of BMI changes

The data for affected children on approximately 8.8% of resident children were collected from 646 boys and 597 girls who attended 97 nursery schools in Fukushima, 904 boys and 854 girls from 132 nursery schools in Miyagi and 483 boys and 458 girls from 81 nursery schools in Iwate. The data for the unaffected children on approximately 12.3% of resident children were collected from 307 boys and 285 girls attending 42 nursery schools in Yamagata, 762 boys and 739 girls from 88 nursery schools in Akita and 638 boys and 634 girls from 108 nursery schools in Aomori.

12. *Presentation of BMI change in each cohort area situation for foods intake and physical activity would be strikingly different between the evacuees because of tsunami and proper habitants of the affected areas. It will be helpful to plot the sampling points and affected area by tsunami on Fig.1. Addition of the data on the proportion of the evacuees in 3 study areas will be helpful because the effects of tsunami and /or those of nuclear power plants accidents in the areas are potentially different.*

We appreciate your helpful suggestion for an improved figure. Because the data were collected from numerous nursery schools without postal codes, we abandoned plotting the addresses in Figure 1. We confirmed that the children resided in the three parts of Fukushima: Hamadori, Nakadori and Aizu. To explain the post-disaster situations, we superimposed the proportions of evacuees on the size of each prefectural population shown in Figure 1.

Figure 1 Affected and unaffected prefectures in northeast Japan.[57] The proportions of evacuees are represented according to the numbers of evacuees in March 2012.[58] The areas of the circles are proportional to the population size.



In this revision, we would like to unify the terminologies, describe detailed *P* values and modify the manuscript for more appropriate English. We also have deleted the description of the results that are presented in Table 1 and the definition of BMI which is widely known, to reduce the word count. We have moved the Supplementary Table 2 to Table 2 in the main text, corresponding to the request of *BMJ Open* Editorial Office.

VERSION 2 – REVIEW

REVIEWER	Shin Amemiya Department of Pediatrics, Saitama Medical University, Japan
REVIEW RETURNED	18-Mar-2016

GENERAL COMMENTS	This paper presents an important information regarding the role of a

	grave disaster on the weight changes in preschool children by the comparison between affected prefectures and unaffected prefectures. The results clearly demonstrated the different outcome of the great east Japan earthquake on overweight or weight-reduction even in affected prefectures. The long-term difference in BMI changes between Fukushima and Miyagi may especially need to be evaluated for the future metabolic influence, since early adiposity rebound and prolonged overweight and obesity have been focused on the adulthood metabolic disturbances. In addition, the influences from dietary supply of carbohydrate-rich meals and the nuclear power plant accident on weight changes should be considered separately between affected prefectures, as well as psychological influence.

REVIEWER	Tetsuro Kobayashi, MD, PhD Director, Okinaka Memorial Institute for Medical Research, Japan
REVIEW RETURNED	15-Mar-2016

GENERAL COMMENTS	The manuscript is well revised. I have no comment.