PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Preschoolers' parent rated health disparities are strongly associated with measures of adiposity in the Lifeways cohort study children
AUTHORS	Shrivastava, Aakash; Murrin, Celine; Kelleher, Cecily

VERSION 1 - REVIEW

REVIEWER	Dr Fiona Mensah Murdoch Childrens Research Institute; Royal Children's Hospital; Department of Pediatrics, University of Melbourne Australia
REVIEW RETURNED	29-Apr-2014

GENERAL COMMENTS	TITLE: This could be more accessible if made more succinct. ABSTRACT: Results: Where the odds ratios are presented for BMI and waist-circumference it needs to be clarified what unit of difference in measurement these refer to, later in the manuscript it is indicated but this is also needed here. Conclusions: The conclusion 'Findings have relevance for developmental health policies.' Is very vague, could a more specific conclusion be drawn from these findings? MAIN TEXT: Introduction: The opening statement 'The development of children is critical to their adult well-being and across the lifecourse even subjective estimates may be useful to reflect objectively measured health.' requires citation or further explanation in support of this. Methods: Representativeness of cohort: The authors describe that 'Mothers at follow-up study did not significantly differ in their baseline BMI from non-responders, suggesting no notable attrition bias.[28,30]'. It is important to also consider how comparable the mothers were with regard to socio-demographic and health factors in relation to the baseline population and to a general population more broadly to consider how these findings may be interpreted and generalised to other populations. It is of concern that the analytic sample of 547 reduces to 303 for the multivariate model. The representativeness of these mothers should also be considered and the reasons for this reduction described, whether this is an accumulation of missing data across a number of variables or due to large amounts of missing data in any specific variables. A consideration of how this may have affected the findings

	should be given, for example may the prevalence of obesity be understated? Terminology: The term ‘shelves’ referring to the shelves defined in the Irish food pyramid is specific to this context, it may be useful to use a term such as ‘category’ in the tables so these may be interpreted more widely and independently from the text. Dichotomisation of measures: A number of the measures are dichotomised such that the most extreme category (e.g. obesity, highest quintile) is compared to the whole of the remaining population. Often we may expect to see a gradient of association with health rather than a dichotomisation of the risk, for example it is likely that children who are overweight may have increased health risks also. Considering the explanatory variables in this way certainly results in a loss of information and their potential explanatory power and may have led to some effects being understated in terms of how statistically significant they are, it may be helpful to consider nominal or ordinal variables with a larger number of categories or to look at trends across the continuum. Results: Table 2: In the first paragraph where the determinants of health that are chose are described it would be more informative to give an indication of the nature of these effects, which are positive and which negative influences and to illustrate with some of the data from Table 2. Table 3: Where table 3 is described it is important that the odds ratios are clearly interpreted as indicating increased or decreased ‘odds’ rather than ‘likelihood’ which may be interpreted as a relative risk. These are not comparable when the prevalence of the outcome is not rare. Also include 95% confidence intervals for the odds ratios to illustrate the precision of the effects. The differences in the estimates given in Table 3 and eTable 2 are concerning. The process of standardising continuous variables should only change the scale and location so the models should be equivalent other than the actual size of these odds ratios and their confidence intervals. The odds ratios for the categorical variables in the model should not be changed. These analyses need to be double checked. I don’t think that eTable2 would be necessary in addition to Table 3 but it would be worth considering whether any of the explanatory variables may be more interpretable if standardised in the main analysis. It would be interesting to see the unadjusted effects of BMI and waist circumference as a starting measure of association and then for comparison to see how much they are attenuated when you account for other health and social factors. It would also be of interest to look at the effects of BMI and waist circumference together within a model to see if they both maintain an important contribution to describing risk of poorer health or one is more critical than another. Discussion: The description of the association between BMI/waist circumference and PRH as ‘temporal’ needs further clarification ‘The observed association between BMI or waist circumference and PRH in the present analysis may be temporal, as demonstrated in adults.[21,22]’. This is similarly mentioned in the introductory sentence and would benefit from clarification ‘The negative

	relationship between obesity and self-rated health is now increasingly reported in adult populations,[19,20] some indicating a temporal relationship[21,22] and suggesting that obesity increases health inequalities over time.[22] Limitations: It is noted that the study is limited by the sample size, it is important to discuss what the implications of this may be, primarily potentially important explanatory factors may have been overlooked because they did not meet the criteria for significance of $p<0.2$. Although this is quite an inclusive cut point there is the concern of residual confounding where important confounders were not considered. It would be preferable to make a decision on confounders a priori on the basis of clinical rationale rather than selecting according to significance level. STROBE CHECKLIST There appear to be items ticked that are either not applicable, e.g. 10. Explain how the study size was arrived at (given this is a secondary analysis), or that haven't been addressed, e.g. 12b. Explain how missing data were addressed. It would be good to review this again and in light of revisions made.

REVIEWER	Gregory Stevens Keck School of Medicine of the University of Southern California
REVIEW RETURNED	05-May-2014

GENERAL COMMENTS	The authors are to be commended for exploring early life experiences and their contribution to child health. This is an important area. But there are several aspects of this study that limit my enthusiasm: 1. The study emphasizes the role of life-course health, but the vast majority of measures come from the same time period (age 5) as the dependent measure. This negates the potential value of longitudinal data in this case, and basically transforms much of this study into a cross-sectional analysis. 2. There is no particularly strong case made for studying parent-reported child health status (PRH). I agree this is a useful measure, but there is very little effort made to justify its focus as the single dependent measure for this study. An example that would build the value of the measure is explaining throughout the frequent absence of clinical or anthropometric data, and so perhaps this global measure could be useful as a proxy. Without some strong argument here, many of the anthropometric and nutrition logs would seem to be equally or more useful as a dependent measure. 3. While the authors mention a life course framework, there is very little in the way of a conceptual model guiding the selection of study variables. This seems mostly to be a widely-cast net in search of some potential determinants of PRH. The fact that only two variables were ultimately related to PRH in the multivariable model is probably the biggest finding, but this is really glossed over in favor of reporting that BMI was a predictor. 4. Perhaps the biggest problem is statistical. Negative PRH was a very rare occurrence, with only 42 children falling into this category (out of 505). This alone may not be a problem, but when we see that

	only 5 children had negative PRH among the obese group, there is almost no way that we could treat any multivariable analyses as reliable. Once you control for other variables, that cell size has to be divided among all the other variables that are included, which creates a major problem here, where the authors are controlling for 20 more variables. My only suggestion is for the authors to either redefine the dependent measure so that there are more relatively negative cases, and to also consider combining obese/overweight into one category. Without these two options and some assessment of the distribution of responses, the authors should probably not trust the findings. And even then, controlling for 20 variables with a sample size of just about 550 is asking a lot of your data, and might require statistical consultation. I suspect this is also why the r-squared is so large…since there are so few negative PRH cases it is potentially easy to predict all of them.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Thank you for the opportunity to review this interesting manuscript. My review particularly focuses on the conduct and presentation of the statistical analyses. I have detailed some comments below that may help in amending and clarifying areas of concern.
Authors Response: Thank you for appreciating and reviewing our manuscript. We have accordingly taken care to amend and improve the manuscript based on your suggestions. The changes have been highlighted in the manuscript with red colour fonts. We also have provided clarifications on your comments in this document.

TITLE:
1. This could be more accessible if made more succinct.
Authors Response: Thank you, we have amended the title as follows: “Preschoolers' parent rated health disparities are strongly associated with measures of adiposity in the Lifeways cohort study children’’

ABSTRACT:
2. Results: Where the odds ratios are presented for BMI and waist-circumference it needs to be clarified what unit of difference in measurement these refer to, later in the manuscript it is indicated but this is also needed here.
Authors Response: The units of BMI (kg/m2) and waist-circumference (cm) have now been indicated in the abstract. The units have also been indicated in the methodology section.

3. Conclusions: The conclusion ‘Findings have relevance for developmental health policies.’ Is very vague, could a more specific conclusion be drawn from these findings?
Authors Response: The conclusion text “Findings have relevance for developmental health policies.” has been replaced with
“The findings suggest that lifecourse adversities during the early developmental stage may get embedded and expressed as anthropometric measures of adiposity, suggesting that public health interventions should begin as early as possible.

MAIN TEXT:
4. Introduction: The opening statement ‘The development of children is critical to their adult well-being and across the lifecourse even subjective estimates may be useful to reflect objectively measured health.’ requires citation or further explanation in support of this.
Authors Response: Four relevant citations have now been included that support the opening

statement in the introduction, including those of seminal contributor, Prof David Barker, suggesting that adult chronic diseases are contributed by the changing pattern of human development. We further cite two other manuscripts which summarises why subjective self-rated health is considered an important and valid measure of objective measures, including morbidity, mortality, longevity and health status.

Methods:
5. Representativeness of cohort: The authors describe that 'Mothers at follow-up study did not significantly differ in their baseline BMI from non-responders, suggesting no notable attrition bias.[28,30]'. It is important to also consider how comparable the mothers were with regard to socio-demographic and health factors in relation to the baseline population and to a general population more broadly to consider how these findings may be interpreted and generalised to other populations.
Authors Response: In previous publications from this cohort we have discussed representativeness. This has now been explicitly added. "A comparison between the Lifeways mothers and a nationally representative sample of women of the same age group from the SLÁN (Survey of Lifestyle, Attitudes and Nutrition) surveys of Republic of Ireland[ref] confirmed that the Lifeways mothers were satisfactorily representative of the Irish general women on socio-demographic characteristics. [ref]"
The section on attrition bias and its discussion in limitation has been edited -
"Though mothers who responded to the follow-up were more likely to be of higher socioeconomic status, these mothers did not significantly differ in their baseline anthropometric characteristics (including BMI) from non-responders.[ref]"
and
"As in most birth cohort studies,[ref] the Lifeways birth cohort also experienced the attrition of mothers belonging to lower socio-economic status in the early stages of the study. Though this may underestimate some socioeconomic inequalities,[ref] it does not negate the exposure-outcome associations detected through regression models of such longitudinal studies.[ref]"

6. It is of concern that the analytic sample of 547 reduces to 303 for the multivariate model. The representativeness of these mothers should also be considered and the reasons for this reduction described, whether this is an accumulation of missing data across a number of variables or due to large amounts of missing data in any specific variables. A consideration of how this may have affected the findings should be given, for example may the prevalence of obesity be understated?
Authors Response: The concerns of small sample size, reduced numbers in multivariate models, missing data, and possible influence on findings, have now been addressed in the paragraph related to limitations.
"Though the study was able to detect the major explanatory domains for child health inequalities documented in the literature [ref], the relatively small sample size of this study may possibly have underpowered it to detect variables with lesser effect sizes. The complete case approach to analysis reduced the sample size of the final multivariate model. However, this missing data was not systematic but rather on account of accumulation of missing completely at random data across a number of variables. It may be argued that the reduced sample size possibly influenced the odds ratio estimate for the association between children's relatively-positive PRH and the child's not being obese (using a categorical IOTF classification). Nonetheless, this association between children's anthropometric measures and their parent-rated health variable is likely to be coherent, because these associations remain statistically significant even when BMI and WC are analysed as continuous variables."

7. Terminology: The term 'shelves' referring to the shelves defined in the Irish food pyramid is specific to this context, it may be useful to use a term such as 'category' in the tables so these may be interpreted more widely and independently from the text.
Authors Response: The term 'shelf' and 'shelves' have been replaced with terms 'food group' and 'food groups' in the tables and this equivalence has also clarified in the methodology section.

8. Dichotomisation of measures: A number of the measures are dichotomised such that the most extreme category (e.g. obesity, highest quintile) is compared to the whole of the remaining population. Often we may expect to see a gradient of association with health rather than a dichotomisation of the risk, for example it is likely that children who are overweight may have increased health risks also. Considering the explanatory variables in this way certainly results in a loss of information and their potential explanatory power and may have led to some effects being understated in terms of how statistically significant they are, it may be helpful to consider nominal or ordinal variables with a larger number of categories or to look at trends across the continuum.
Authors Response: We agree this is an important point. In fact, during preliminary analyses all independent variables with continuous data, the anthropometric and food/nutrient related variables, were analysed both as continuous variables as well as categorical variables. The Table 2 of the manuscript shows the results for all anthropometric measures analysed as continuous data. Only the variable of interest, the BMI, has been presented as both continuous and categorical variables.
The anthropometric and food/nutrient variables that qualified for $p<0.2$ significance levels qualified so irrespective of being analysed as continuous variables or as categorical variables. The results for food/nutrient variables analysed as continuous data has not been shown in the Table 2 of the manuscript, for reasons of brevity.
Dichotomisation of variables has three purposes. Firstly, the comparison of the furthest category (extreme quintile or the obese) against the others was easier to interpret. Secondly, such comparison with the most extreme level gave better statistical significance, suggesting that effect sizes are larger when such starkly different subgroups are contrasted. Thirdly, this analysis of lifecourse adversities already looked into a large number of lifecourse variables at univariate level, and if each of these variables had been spread out into more number of categories, instead of dichotomisation, it would have compromised the model, requiring a larger sample size to satisfy requirements of each cell in the contingency table.

Results:
9. Table 2: In the first paragraph where the determinants of health that are chose are described it would be more informative to give an indication of the nature of these effects, which are positive and which negative influences and to illustrate with some of the data from Table 2.
Authors Response: The explanations for Table 2 are now additionally described such as to give an indication of the positive and negative direction of these effects, along with odds ratio data.
“In other words, retaining $p<0.2$ as the criterion for significance, the children’s healthy food and nutrient intake habits – such as decreased intake of unhealthy fat- and sugar- rich foods (servings/day) [OR(95%CI)=1.7(0.8-3.4)] or total fats (g) in their meals [OR(95%CI)=2.2(1.1-4.3)] and increased intake of healthy fruits and vegetables (servings/day) [OR(95%CI)=2.2(1.1-4.3)] were positively associated with their favourable rating for health by their mothers. Conversely, children’s increased BMI (kg/m2) [OR(95%CI)=0.85(0.71-1.03)] and waist circumference (cm) [OR(95%CI)=0.95(0.88-1.02)] were inversely associated with a positive parental-rated health status.” and
“In other words, by maintaining $p<0.2$ as the criterion for significance, several indicators of a family’s better socio-economic status– such as increased household income (Euros/week) [OR(95%CI)=3.0(1.6-5.9)], not requiring subsidised healthcare [OR(95%CI)=2.1(1.0-4.3)], mother having a third level education [OR(95%CI)=1.9(1.0-3.6)], father having a third level education [OR(95%CI)=1.9(1.0-3.6)], father being self-employed [OR(95%CI)=2.5(0.8-7.9)]; family’s better psycho-social status– such as father’s involvement in family affairs [OR(95%CI)=2.1(1.0-4.3)], mother’s perceiving a positive social support from spouse [OR(95%CI)=2.3(1.2-4.3)], parents [OR(95%CI)=2.0(1.0-4.1)], children [OR(95%CI)=1.9(1.0-3.7)], or relatives [OR(95%CI)=2.2(1.1-4.1)]; family’s better lifestyle and food and nutrient intake habits– such as mother’s decreased intake of unhealthy fat- and sugar- rich foods (servings/day) [OR(95%CI)=1.7(0.8-3.4)], total energy (kcal) [OR(95%CI)=2.2(1.1-4.3)] and total fats (g) [OR(95%CI)=1.7(0.8-3.4)] in her meals, father’s not being

a smoker [OR(95%CI)=2.2(1.1-4.4)]; and family's better health status– such as mother [OR(95%CI)=5.1(2.6-9.9)] and father [OR(95%CI)=3.0(1.5-6.0)] having a positively rated health status were positively associated with children's favourable rating for health by their mothers."

10. Table 3: Where table 3 is described it is important that the odds ratios are clearly interpreted as indicating increased or decreased 'odds' rather than 'likelihood' which may be interpreted as a relative risk. These are not comparable when the prevalence of the outcome is not rare. Also include 95% confidence intervals for the odds ratios to illustrate the precision of the effects.
Authors Response: The term 'likelihood' has been replaced with term 'decreased odds' and 95% confidence intervals for the odds ratios have been shown in the text.

11. The differences in the estimates given in Table 3 and eTable 2 are concerning. The process of standardising continuous variables should only change the scale and location so the models should be equivalent other than the actual size of these odds ratios and their confidence intervals. The odds ratios for the categorical variables in the model should not be changed. These analyses need to be double checked.
12. I don't think that eTable2 would be necessary in addition to Table 3 but it would be worth considering whether any of the explanatory variables may be more interpretable if standardised in the main analysis.
Authors Response: One of the objectives of our analysis, as we highlight in the introduction, is "to examine whether anthropometric markers of child obesity would emerge as strong predictors of global health status when accounted for other socio-economic, psycho-social, and lifestyle environmental factors in a multivariable model." This additional standardised odds ratio analysis was done to help in interpretation of this strength of association across analysed independent variables. The results were re-checked using STATA, which provides a "listcoef" command for both the unstandardised odds ratio "e^b" and the standardised odds ratios "e^bStdX", explained as odds ratios for standard deviation change in the independent variable. It is agreed that such standardized coefficients are generally not very intuitive, and therefore as suggested, eTable2 has been removed and only the line in the text has been retained.

13. It would be interesting to see the unadjusted effects of BMI and waist circumference as a starting measure of association and then for comparison to see how much they are attenuated when you account for other health and social factors.
Authors Response: Whereas the unadjusted associations of children's BMI and waist circumference with their PRH have been shown in Table 2, the adjusted effects have been shown in Table 3. The unadjusted odds ratio for BMI (analysed as a categorical variable – IOTF classification) was 2.69 (0.96-7.54) (Table 2) which on adjustments changed to 5.48 (1.43-21.03) (Table 3). When BMI (kg/m2) was analysed as a continuous variable, the unadjusted odds ratio of 0.85 (0.71-1.03) (Table 2) changed to 0.73 (0.58-0.93) on adjustments (Table 3). The unadjusted odds ratio for waist circumference (cm) analysed as continuous variable was 0.95 (0.88-1.02) (Table 2) which on adjustments changed to 0.89 (0.81-0.98) (Table 3). "Thus the association between children's BMI or waist circumference and their PRH only strengthened following adjustments in this multivariate model, irrespective of being analysed as a categorical or continuous variable." This last expression has now been added to the paragraph explaining results of Table 3.

14. It would also be of interest to look at the effects of BMI and waist circumference together within a model to see if they both maintain an important contribution to describing risk of poorer health or one is more critical than another.
Authors Response: Studies that have analysed development of body composition and related variables, inclusive of BMI and waist circumference, have found complex interactions among these variables. In this study BMI and waist circumference were analysed in separate models and not together within a model as results of interaction would be difficult to interpret. Relevant citations have

been provided below.
a. Rogers I and the EURO-BLCS Study Group. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. Int J Obes Relat Metab Disord 2003;27(7):755-77.
b. Wells JC, Chomtho S, Fewtrell MS. Programming of body composition by early growth and nutrition. Proc Nutr Soc 2007;66(3):423-34.

Discussion:
15. The description of the association between BMI/waist circumference and PRH as 'temporal' needs further clarification 'The observed association between BMI or waist circumference and PRH in the present analysis may be temporal, as demonstrated in adults.[21,22]'.
Authors Response: This has now been further clarified by further adding the following paragraph in discussion section – "Though a number of large scale cross sectional studies have shown an association between anthropometric measures of obesity and self rated health,[ref] only recently a few nationally representative prospective studies have established the temporality of this association in adults.[ref] Though this relationship maybe bi-directional to an extent,[ref] the mounting evidence from longitudinal birth cohort studies regarding a sequential relationship between lifetime growth trajectories and adult disease, disability and deaths[ref] primarily rules out reverse causality in this association and suggests that the association observed in our birth cohort is also more likely to be temporal. More so, findings from a few longitudinal studies available on primary school age children suggest that at least in the childhood this inverse association found between BMI and HRQoL is predominantly in the given direction and not the reverse.[ref]"

16. This is similarly mentioned in the introductory sentence and would benefit from clarification 'The negative relationship between obesity and self-rated health is now increasingly reported in adult populations,[19,20] some indicating a temporal relationship[21,22] and suggesting that obesity increases health inequalities over time.[22]
Authors Response: Now further clarification on this has been provided in the discussion section. See response to the previous paragraph №15.

17. Limitations: It is noted that the study is limited by the sample size, it is important to discuss what the implications of this may be, primarily potentially important explanatory factors may have been overlooked because they did not meet the criteria for significance of $p<0.2$.
Authors Response: This concern of small sample size has been addressed in the limitations sections. Also see response to the paragraph №6 above.
"Though the study was able to detect the major explanatory domains for child health inequalities documented in the literature [ref], the relatively small sample size of this study may possibly have underpowered it to detect variables with lesser effect sizes."

18. Although this is quite an inclusive cut point there is the concern of residual confounding where important confounders were not considered. It would be preferable to make a decision on confounders a priori on the basis of clinical rationale rather than selecting according to significance level.
Authors Response: The Lifeways database has a large number of variables available. However, only a limited number of variables were chosen for this analysis based on their relevance documented in the published literature - this was a priori decision about selection of variables from distinct domains of child's individual and family spheres of influence on their development. The $p<0.2$ analysis helped to reduce the list to 20 variables for the final model. The final model still included variables from known domains of child's individual and family spheres of influence on their development.
This has been stated in two paragraphs of the methodology section -
"Thus variables from discrete stages (pre-pregnancy, early pregnancy, at birth, early infancy and 5-year follow-up) of child's early development representing lifecourse exposures from distinct domains

(demographic, anthropometric, socio-economic, psycho-social, lifestyle, nutritional and health) of child's individual and family spheres of influence[ref] were considered to analyse determinants of child's health status at age-5. The selection of variables, domains and spheres of influence are based on the CSDH constructed TEAM-ECD, a model of early child development.[ref]"
and
"From these independent variables principally chosen on the basis of their relevance to the child's development,[ref] all those that qualified at significance level 20% ($p<0.2$)[ref] in univariate analyses were force entered into a multivariable logistic regression model."

STROBE CHECKLIST
19. There appear to be items ticked that are either not applicable, e.g. 10. Explain how the study size was arrived at (given this is a secondary analysis),
Authors Response: The item has been unticked.

20. or that haven't been addressed, e.g. 12b. Explain how missing data were addressed.
Authors Response: The type of missing data and use of a complete case approach for regression analysis has now been mentioned in the limitations section.

21. It would be good to review this again and in light of revisions made.
Authors Response: Thank you for considering reviewing our manuscript once again. We are hopeful that you will find the manuscript with revisions satisfactory.

Reviewer 2
The authors are to be commended for exploring early life experiences and their contribution to child health. This is an important area. But there are several aspects of this study that limit my enthusiasm:
Authors Response: We thank you for appreciating the relevance of this topic of our research and for reviewing our manuscript. We have made efforts to further develop the manuscript utilising your suggestions and provide clarifications where required in this document. The changes in the manuscript have been highlighted using red colour fonts.

22. The study emphasizes the role of life-course health, but the vast majority of measures come from the same time period (age 5) as the dependent measure. This negates the potential value of longitudinal data in this case, and basically transforms much of this study into a cross-sectional analysis.
Authors Response: This is a longitudinal study recruited during pregnancy. We agree that a number of independent variables in this study pertain to same time period (age 5) as the dependent measure and prove to be relevant predictors of outcome. However, as shown in Table 1, quite a number of variables also pertain to potentially relevant discrete earlier stages of the child's life: pre-pregnancy, early pregnancy, at birth, and early infancy. Not many birth cohorts have the availability of all these important variables together required to demonstrate how exposures of early development, specifically those up to early infancy, influence health of a young preschooler.

23. There is no particularly strong case made for studying parent-reported child health status (PRH). I agree this is a useful measure, but there is very little effort made to justify its focus as the single dependent measure for this study. An example that would build the value of the measure is explaining throughout the frequent absence of clinical or anthropometric data, and so perhaps this global measure could be useful as a proxy. Without some strong argument here, many of the anthropometric and nutrition logs would seem to be equally or more useful as a dependent measure.
Authors Response: With respect, we disagree. The senior author on this paper designed the study to assess how global measures of health status relate to other domains and parent–rated health status

of children is an established and validated measure.
Specifically:
a) In the introduction, we state that the objectives of our analysis were to examine the predictors of child's global health status and also whether child obesity was a strong predictor of this dependent measure. Also, the major findings in relation to these two a priori objectives are stated in the first paragraph of the discussion section -
"Thus the first objective of our analysis was to prospectively examine the relationship between demographic, anthropometric, lifestyle, nutritional, psycho-social, socio-economic and health-related lifecourse exposures taken from the children's individual and family spheres of influence starting from preconception up to age 5-years and their global health status at preschool-age."
and
"The next objective of our analysis was to examine whether anthropometric markers of child obesity would emerge as strong predictors of global health status when accounted for other socio-economic, psycho-social, and lifestyle environmental factors in a multivariable model."
b) Secondly, in the introduction section we explain that this dependent measure has previously been used to examine life-course determinants but is less well studied in preschool-age children -
"Based on this, Hertzman and colleagues[ref] examined self-rated health in adulthood using an integrated lifecourse framework. There are a few other studies also which have examined lifecourse determinants of adult global[ref] or specific health status.[ref] On the contrary, the literature on the determinants of child global health status is sparse, [ref] particularly for the preschool-age children.[ref] Even rarer are studies whose examination includes early lifecourse determinants of child global health status."
c) Then, in the discussion section we further build on the argument about obesity being an early phenotypic expression of lifecourse adversities and about the temporal association between obesity and dependent measure global health status (edits have been made to the manuscript to further clarify temporality in association) -
"The Lifeways previously demonstrated longitudinal association between parental socio-economic and lifestyle characteristics and child's BMI and waist circumference. [ref] In this analysis when same anthropometric measures are included along-with material, psycho-social, and lifestyle determinants of child obesity and health, a prominent relationship emerges between children's anthropometric measures and health status. One possible explanation is that determinants of health inequalities biologically embed[ref] in early life and child obesity is an early phenotypic expression of this inequality; though the continued influence of environmental factors is not undermined. Adult[ref] and adolescence studies[ref] have also shown this association to be independent of socio-demographic, lifestyle or health-related factors."
See response to the paragraph №15 above about temporal association between obesity and dependent measure global health status.
d) In the discussion section we also provide citations on the importance and validity of self-rated health and its parental proxy as a measure (edits have been made to the manuscript to further clarify importance of this measure over usual objective measures)-
"Self-rated health is an important and valid measure of morbidity, mortality, longevity and health status, [ref] also in Irish adult[ref] and children.[ref] It is believed to be a more inclusive measure of health than the objective measurements, with a capacity to comprehensively evaluate health dynamics, behaviours and psycho-physiological states that are not otherwise easy to measure.[ref] This holistic measure better accommodates the WHO defined concept of health as opposed to a diagnosed specific disease.[ref] Use of parent proxy for child self-reported health is justified for children too young to have adequate cognitive skills.[ref] Systematic reviews report good agreement between ratings by children and their parents on child HRQoL, particularly for physical health domain.[ref] Parents tend to be thoughtful when responding to proxy questions and report children's usual health disposition.[ref] Studies on construct validity report positively.[ref] Maternal ratings of child's general health status were found sensitive when validated against children's illnesses and other morbidity or healthcare indicators,[ref] including evidence of a gradient in strength of these

associations.[ref] Many national-level studies have accepted parent proxy as an appropriate measure[ref] and successfully used it to longitudinally demonstrate risk and consequences of child health.[ref]"

24. While the authors mention a life course framework, there is very little in the way of a conceptual model guiding the selection of study variables. This seems mostly to be a widely-cast net in search of some potential determinants of PRH. The fact that only two variables were ultimately related to PRH in the multivariable model is probably the biggest finding, but this is really glossed over in favor of reporting that BMI was a predictor.
Authors Response: Again, with respect, we disagree. The study was established to assess determinants of childhood growth and development and a comprehensive dataset was accordingly collected from pregnancy to age 5. We even state the purpose of establishing this cohort in the methods section of the paper "The a priori purpose was to examine familial and cross-generation influences on early childhood development over the first five years of children's lives."
a) In the introduction section we introduce the models of Bronfenbrenner and the WHO formulated "Total environment assessment model for early child development" which are popular conceptual models that guide selection of domains and variables for child health studies. We then in our methodology section specify that we chose the variables from domains specified under the latter model (edits have been made to the manuscript to further clarify this) -
"Recently, the World Health Organisation's (WHO) Commission on Social Determinants of Health (CSDH) presented a Total Environment Assessment Model for Early Child Development (TEAM-ECD),[ref] which again illustrates the importance of individual and family spheres of influence on children's health."
and
"Thus variables.....of child's early development representing lifecourse exposures from distinct domains (demographic, anthropometric, socio-economic, psycho-social, lifestyle, nutritional and health) of child's individual and family spheres of influence[ref] were considered to analyse determinants of child's health status at age-5. The selection of variables, domains and spheres of influence are based on the CSDH constructed TEAM-ECD, a model of early child development.[ref]"
b) Secondly, in the introduction section we introduce the lifecourse framework concept and relevance of certain stages and transition periods in context of vulnerability of the individual to environmental insults. In the methodology section we specify that we chose and arranged the variables from lifecourse stages and transition periods relevant from a young child's health development perspective (edits have been made to the manuscript to further clarify this) -
"According to the lifecourse hypothesis, risk transmission is characterised by critical periods and accumulation of risk models.[ref] Life Course Health Development (LCHD) framework[ref] suggests that health is a consequence of multiple determinants that change in context of time and circumstances as an individual develops; these experiences are programmed into bio-behavioural regulatory systems during certain critical and sensitive periods of individual's lifetime to decide their health trajectory. The lifecourse framework on childhood disadvantage and adult health[ref] suggests that parental and childhood circumstances from the point of conception influences individual's health in later life, and the individual's childhood health and later life circumstances may further add to this foundation. Based on this, Hertzman and colleagues[ref] examined self-rated health in adulthood using an integrated lifecourse framework."
and
"Thus variables from discrete stages (pre-pregnancy, early pregnancy, at birth, early infancy and 5-year follow-up) of child's early development representing lifecourse exposures.....were considered to analyse determinants of child's health status at age-5. .....These lifecourse variables have been summarised as per time frame in Table 1. This lifecourse time frame highlights the stages and transition points relevant from perspective of child's health development. [ref]"
c) In the response to your previous comment, we have explained why we consider the relationship with BMI is relevant.

“One possible explanation is that determinants of health inequalities biologically embed[ref] in early life and child obesity is an early phenotypic expression of this inequality; though the continued influence of environmental factors is not undermined.”

25. Perhaps the biggest problem is statistical. Negative PRH was a very rare occurrence, with only 42 children falling into this category (out of 505). This alone may not be a problem, but when we see that only 5 children had negative PRH among the obese group, there is almost no way that we could treat any multivariable analyses as reliable. Once you control for other variables, that cell size has to be divided among all the other variables that are included, which creates a major problem here, where the authors are controlling for 20 more variables. My only suggestion is for the authors to either redefine the dependent measure so that there are more relatively negative cases, and to also consider combining obese/overweight into one category. Without these two options and some assessment of the distribution of responses, the authors should probably not trust the findings. And even then, controlling for 20 variables with a sample size of just about 550 is asking a lot of your data, and might require statistical consultation. I suspect this is also why the r-squared is so large…since there are so few negative PRH cases it is potentially easy to predict all of them.
Authors Response: Thank you, we agree that if we were to solely rely on this observation with small numbers of obese cases there would be a concern. However, we also observed this association across the distribution of body weight.
a) We agree with the limitation of having just 5 obese children in the negative PRH group - we argue in the discussion section that having analysed BMI and WC as continuous variables (which is not affected by the limitation of subgroup sampling) and having found them statistically associated, we have possibly addressed the limitation related to the analysis of BMI as a categorical variable resulting in small numbers of obese children–
“It may be argued that the reduced sample size possibly influenced the odds ratio estimate for the association between children’s relatively-positive PRH and the child’s not being obese (using a categorical IOTF classification), Nonetheless this association between children’s anthropometric measures and their parent-rated health variable is likely to be coherent, because these associations remain statistically significant even when BMI and WC are analysed as continuous variables”
b) We judged the sample size in our analysis on the criteria defined by Long (1997) for Maximum Likelihood Estimation (MLE): sample size should not be smaller than 100, while those over 500 would be considered adequate and that it would be reasonable to have at least 10 observations per parameter. All the same, we still agree that the relatively small sample sizes in study may have limitations and therefore we acknowledged this limitation in our discussion.
c) Pertinently, we actually run the risk of making a Type II error i.e. missing a few possible true predictors as the number of independent variables increases in a small sample MLE study. The risk of making Type I error i.e. making a false positive predictor is not appreciably affected by small sample sizes in a MLE analysis. Thus we can be quite sure of the statistically significant findings of our analysis even if we may have doubts about any other true predictor having not reached the level of statistically significance on account of sample size limitation (Hart RA & Clark DH 1999).
d) As for the suggestion of redefining the dependent measure so that there are more relatively negative cases we state in the methodology section -
“The 5-graded scale response was dichotomised as relatively-positive health (excellent or very good) and relatively-negative health (poor or fair or good), based on similar dichotomisation in other studies on preschool and school children.[ref] It is reasonable to take a higher cut-off when dichotomising this age dependent variable in this very young age-group as there would be very limited numbers of poor or fair health children.[ref]”
It would be problematic in our view to also shift the “very good” into the relatively-negative health category.
e) As for the suggestion of considering combining obese/overweight into one category we found that only comparison with the most extreme levels gave better statistical significance, suggesting that effect sizes are larger and easily noticeable when such starkly different subgroups are contrasted.

Moreover, as the analysis of BMI and WC as continuous variables gave statistical significant results, the limitation of analysing BMI as categorical variable in a small sample was reasonably addressed.
f) We would also like to apprise that the Hosmer and Lemeshow test for goodness of fit in all the three final models were p=0.23, p=0.38, p=0.25 suggesting that the models fitted the data properly.
Hart RA and Clark DH. "Does size matter? Exploring the small sample properties of maximum likelihood estimation." In Annual Meeting of the Midwest Political Science Association. 1999.
Long JS. Regression Models for Categorical and Limited Dependent Variables. Vol. 7 of Advanced Quantitative Techniques in the Social Sciences. Thousand Oakes CA: Sage, 1997: p297
Thank you once again. We are hopeful that you will find the clarifications and revisions in the manuscript acceptable.

VERSION 2 – REVIEW

REVIEWER	Dr Fiona Mensah Murdoch Childrens Research Institute Royal Children's Hospital Department of Pediatrics, University of Melbourne All Australia
REVIEW RETURNED	19-Jun-2014

GENERAL COMMENTS	Reviewer 1: Point 6: It is too strong an assumption that the missing data would be 'missing completely at random'. It would be recommended to note that the missing data was on account of an accumulation across a number of variables and whether there is any evidence of selectivity in the participants for whom there were missing data. Point 9: It would be recommended to use the terminology 'higher' or 'lower' rather than 'increased' or 'decreased' when describing the effects associated with risk factors for the children. Increased or decreased may imply change over time within an individual child rather than magnitude relative to peers. Point 10: Similarly it would be preferable to refer to 'lower odds' rather than 'decreased odds'. Point 14: It would be valuable to include this comment and the citations in the manuscript as others may also be interested.

REVIEWER	Gregory Stevens University of Southern California
REVIEW RETURNED	21-Jun-2014

GENERAL COMMENTS	This revision is an improvement on the first. The authors have made an effort to respond to many of the reviewers' comments, but I still have three concerns. 1. How the analysis is conducted given the relatively sample size I think is still likely to be a problem. The fact that only 2 out of 20 variables that were anticipated to predict child global health, were actually found to be significant in the multivariable model is probably evidence that the analysis is underpowered. Ideas to help still include redefining the child global health in a way that improves the distribution of responses (e.g., "excellent" vs. "else), more parsimoniously selecting the study covariates, and taking steps to

	re-include more of the 547 children. For example, if you choose a smaller set of covariates, it is likely that fewer children will be dropped from the analysis since there are fewer variables for cases to be missing. A very small additional point regarding sample size: the abstract mentions over 1,082 families, but it might be better to report the actual analytic sample (n=547) consistently throughout? 2. If the analysis strategy has not led to the study being underpowered, then the relationship between BMI (and maternal global health) and child global health is probably overshadowed by another finding of this paper. The more striking result is that so little else about a child's early childhood experience actually affects their global health. That result is opposite to the what the authors set-up and anticipated in the introduction, and so might deserve a fuller discussion. 3. I'm not entirely sure that the new set of implications is the most cautious interpretation of the data. The authors write, "The findings suggest that lifecourse adversities during the early developmental stage may get embedded and expressed as anthropometric measures of adiposity, suggesting that public health interventions should begin as early as possible." If the authors are saying that BMI could be expressing some portion of the negative childhood experiences that affect the child's global health, then isn't this something the authors could be testing in their analyses (e.g., a model with and without BMI included)? Without this, it might be better to stick to more direct implications: e.g., to focus on reducing childhood obesity and maternal health as ways to improve child global health). I sincerely hope these critiques help as I would like to see these outstanding authors build a resilient analysis that advances the field. If it would be helpful or the authors feel I'm being just a bit too stubborn regarding their results, I would have no problem with the journal considering seeking an alternate reviewer.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

Thank you for your thorough revisions, I am very happy that my suggestions have been addressed comprehensively. I have just a few minor suggestions for further revision as detailed to follow.

Authors' response (AR): Thank you for your suggestion. The manuscript has now accordingly been revised. The changes have been highlighted as red colour fonts in the marked copy of the manuscript. The line numbers are also provided in the marked copy.

Point 6: It is too strong an assumption that the missing data would be 'missing completely at random'. It would be recommended to note that the missing data was on account of an accumulation across a number of variables and whether there is any evidence of selectivity in the participants for whom there were missing data.

AR: We have removed the term 'missing completely at random' in write up and just mention that "missing data was on account of an accumulation across a number of variables. On analysis, there was no evidence of selectivity in the participants for whom there were missing data (eTable 2)."

(please see the eTable 2 also included below).
(Line numbers 6 to 12 on Page 21)

Point 9: It would be recommended to use the terminology 'higher' or 'lower' rather than 'increased' or 'decreased' when describing the effects associated with risk factors for the children. Increased or decreased may imply change over time within an individual child rather than magnitude relative to peers.

AR: This has been changed in the text. (Line numbers 22, 24 on Page 11 and 2,13, 21 on Page 12)

Point 10: Similarly it would be preferable to refer to 'lower odds' rather than 'decreased odds'.

AR: This has been changed in the text. (Line numbers 5 and 7 on Page 16)

Point 14: It would be valuable to include this comment and the citations in the manuscript as others may also be interested.

AR: This has been included in the text with citations. (Line numbers 3 to 7 on Page 11)

Reviewer: 2

This revision is an improvement on the first. The authors have made an effort to respond to many of the reviewers' comments, but I still have three concerns.

Authors' response (AR): Thank you for your suggestions. The changes have been highlighted as red colour fonts in the marked copy of the manuscript. The line numbers are also provided in the marked copy.

1. How the analysis is conducted given the relatively sample size I think is still likely to be a problem. The fact that only 2 out of 20 variables that were anticipated to predict child global health, were actually found to be significant in the multivariable model is probably evidence that the analysis is underpowered. Ideas to help still include redefining the child global health in a way that improves the distribution of responses (e.g., "excellent" vs. "else), more parsimoniously selecting the study covariates, and taking steps to re-include more of the 547 children. For example, if you choose a smaller set of covariates, it is likely that fewer children will be dropped from the analysis since there are fewer variables for cases to be missing.

AR: Thank you again for these suggestions. We previously responded that in our view it would be inappropriate to dichotomise responses as "excellent" versus the rest i.e. shift the "very good" into the relatively-negative health category. Our a priori hypothesis was that a number of domains could be influential on parent rated health and at univariate level many of them were, which would indicate that power is not an issue at that level (Table 2 on page 14-15).
The fact that the final analysis does not retain more of these as significant could be explained by power considerations including missing variables (which we explicitly accept as a limitation in the manuscript - Line numbers 4 to 6 on Page 21), or alternatively that these factors are possibly mediated through maternal self rated health and child's obesity, which are the final significant predictors. This is quite plausible given what is known in the literature about the social patterning of these variables. In response to the concerns of both reviewers we now provide an additional table in the supplement file which compares children included and not included in the final model for variables belonging to explanatory domains (please see the eTable 2 also included below). This table suggests that there were no significant differences in the characteristics of children included and not included

(due to missing data) for analysis, suggesting that the children in the final model are representative of the study participants as a whole. (Line numbers 6 to 12 on Page 21)

A very small additional point regarding sample size: the abstract mentions over 1,082 families, but it might be better to report the actual analytic sample (n=547) consistently throughout?

AR: This has been changed in the abstract text. (Line numbers 14-15 on Page 2)

2. If the analysis strategy has not led to the study being underpowered, then the relationship between BMI (and maternal global health) and child global health is probably overshadowed by another finding of this paper. The more striking result is that so little else about a child's early childhood experience actually affects their global health. That result is opposite to the what the authors set-up and anticipated in the introduction, and so might deserve a fuller discussion.

AR: As we outlined above, a plausible explanation is that the influence of these factors is mediated through the two significant factors, rather than independently predictive. The other factors were predictive in univariate models but not in multivariate model.

3. I'm not entirely sure that the new set of implications is the most cautious interpretation of the data. The authors write, "The findings suggest that lifecourse adversities during the early developmental stage may get embedded and expressed as anthropometric measures of adiposity, suggesting that public health interventions should begin as early as possible." If the authors are saying that BMI could be expressing some portion of the negative childhood experiences that affect the child's global health, then isn't this something the authors could be testing in their analyses (e.g., a model with and without BMI included)? Without this, it might be better to stick to more direct implications: e.g., to focus on reducing childhood obesity and maternal health as ways to improve child global health).

AR: We agree and the text has been changed as suggested – “The findings suggest that reducing childhood obesity and improving maternal health may be useful ways to improve child global health.” (Line numbers 17-18 on Page 3)

I sincerely hope these critiques help as I would like to see these outstanding authors build a resilient analysis that advances the field. If it would be helpful or the authors feel I'm being just a bit too stubborn regarding their results, I would have no problem with the journal considering seeking an alternate reviewer.

AR: We have found the comments very helpful and have made significant alterations to the paper based on these suggestions. In particular, we have addressed explicitly the limitations of our analysis.

Table: Comparative characteristics of children included and not included in the final model (with and without missing data) for selective variables from each of the explanatory domains - (PLEASE SEE THIS TABLE IN PDF SUPPLEMENTARY DOCUMENT UPLOADED)

S.No., Variables, Children not in the Final Model (With Missing Data, n=244), Children in the Final Model (Without Missing Data, n=303), Sub-categories - n (%) - n (%), Statistic (chi-square or t-test), p-value

OUTCOME VARIABLE

1. Parent rated health status of the Child

Good+Fair+Poor 19 (7.8%), 23 (7.6%)
Excellent+Very Good 225 (92.2%), 280 (92.4%) 0.01 0.93

INDEPENDENT VARIABLES

ANTHROPOMETRIC VARIABLES

2.Child BMI categorised by IOTF classification
Obese 10 (6.2%), 20 (6.6%)
Overweight plus Normal 151 (93.8%), 283 (93.4%) 0.03 0.87

3. Child BMI (continuous) kg/m2,
Mean (Std Dev), 16.73 (1.53), 16.57 (1.74) 0.96 0.34

4. Child waist circumference (continuous) cm,
Mean (Std Dev), 55.95 (4.49), 55.97 (4.54) 0.06 0.95

NUTRITION VARIABLES

4. Top food group consumed by Child (servings/d)
Quintile 5, 46 (18.9%), 64 (21.1%)
Quintiles1-4, 198 (81.1%), 239 (78.9%) 0.43 0.51

5. Top food group consumed by Mothers (servings/d)
Quintile 5, 46 (19.0%), 63 (20.8%)
Quintiles1-4, 196 (81.0%), 240 (79.2%) 0.27 0.61

BEHAVIOUR VARIABLES

6. Father's smoking,
Smoker 58 (26.6%), 81 (26.7%)
Non-Smoker 160 (73.4%), 222 (73.3%) 0.01 0.97

HEALTH VARIABLES

7. Father's health status rating,
Good+Fair+Poor 69 (33.3%), 90 (29.7%)
Excellent+Very Good 138 (66.7%), 213 (70.3%) 0.76 0.39

8. Mother's health status rating,
Good+Fair+Poor 79 (32.5%), 79 (26.1%)
Excellent+Very Good, 164 (67.5%), 224 (73.9%) 2.72 0.10

SOCIO ECONOMIC VARIABLES

9. Father’s Education,
Lower, 64 (30.3%), 80 (26.4%)
Third level, 147 (69.7%), 223 (73.6%) 0.95 0.33

10. Father's employment status
Not Earning, 44 (20.5%), 43 (14.2%)
Employed, 117 (54.4%), 186 (61.4%)

Self employed, 54 (25.1%), 74 (24.4%) 4.02 0.13

PSYCHO-SOCIAL VARIABLES

11.Support from Parents
Lesser support, 33 (17.9%), 63 (20.8%)
More support, 151 (82.1%), 240 (79.2%) 0.59 0.44