

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Sociodemographic predictors of early postnatal growth: evidence from a Chilean infancy cohort.
<b>AUTHORS</b>	Von Holle, Ann; North, Kari; Gahagan, Sheila; Burrows, Raquel; Blanco, Estela; Lozoff, Betsy; Howard, Annie Green; Justice, Anne; Graff, Misa; Voruganti, V. Saroja

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Miaobing Zheng Deakin University, Australia
<b>REVIEW RETURNED</b>	27-Nov-2019

<b>GENERAL COMMENTS</b>	<p>This study examined the sociodemographic determinants of infant growth in the early postnatal period. I have provided some comments to improve clarity of the manuscript.</p> <p>Abstract</p> <ul style="list-style-type: none"><li>• Objectives: Replace “early life environment factors” with “sociodemographic factors”</li></ul> <p>Results:</p> <ul style="list-style-type: none"><li>• The first three lines of results should be method.</li><li>• Were education and SEP examined as separate covariate? Education is usually used as a proxy for SEP. Good to clarify how different are education and SEP in your study.</li><li>• Did you account for infant feeding or other maternal factors such as maternal body weight status, smoking in your analysis?</li><li>• You presented results on velocity and growth timing, what about results for size?</li><li>• In line with your aim, results on gestational age, maternal age and education should be presented as well.</li></ul> <p>Conclusion:</p> <ul style="list-style-type: none"><li>• Please be specific about how the findings of your study would inform prevention efforts aimed at infant growth.</li></ul> <p>Strengths and limitations of the study</p> <ul style="list-style-type: none"><li>• I don't think the monthly measurement of anthropometrics in the first five postnatal months is a strength. Instead, it should be a limitation as other infant growth studies have much longer follow-up into childhood or adolescence.</li><li>• Please provide some details as to what you meant by detailed measure of SEP. What SEP measure was used and why it is better.</li></ul> <p>Introduction</p> <ul style="list-style-type: none"><li>• Please comment more on why looking at the relationship between SEP and earliest period of infant growth is important. Extensive studies look at correlates of growth from infancy to childhood/adolescence and this studies would provide a broader picture on the research question, why these studies do not suffice.</li></ul>
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	<p>Stronger rationale for examining earliest period of infant growth is needed.</p> <ul style="list-style-type: none"> <li>• Provide some context as to why you hypothesize that SEP will be inversely associated with weight gain and positively associated with length gain. In low and middle income countries, this might not be the case, for example, higher SEP may be linked with higher weight gain.</li> </ul> <p>Method</p> <ul style="list-style-type: none"> <li>• Was total years of education included as part of Graffar index?</li> <li>• Please clarify what do multiple comparisons mean?</li> </ul> <p>Results</p> <ul style="list-style-type: none"> <li>• Exclusion of pre-term infants does not fit with the rest of sentence describing the cohort. The exclusion should be mentioned in the methods and in results when describing the final sample size being included in the analysis before description of cohort characteristics.</li> <li>• Weight trajectories: Results on maternal age from unadjusted model were reported. What about results from the adjusted model? For gestational age, results from adjusted model were reported, but not unadjusted. The reporting of results should follow a consistent manner, i.e. reporting unadjusted then adjusted, not picking out significant associations and report those. Where are the results for SEP and weight trajectories?</li> <li>• Length trajectories: 'In the pooled group': do you mean overall sample without stratification by sex?</li> </ul> <p>Discussion</p> <ul style="list-style-type: none"> <li>• The first paragraph, where are the results on maternal age and gestational age? Where are the summary of findings on weight trajectories? The summary of findings should directly answer your aim.</li> <li>• Please provide more details on the mechanisms: how breastfeeding and maternal smoking influence infant growth. Did you explore maternal smoking status and breastfeeding in your analysis? If not, these should be mentioned as limitation.</li> <li>• Page 8 line 5-8: Have you reported any results on SEP and weight trajectories? When compare with other studies, you need provide some details and references for those studies.</li> <li>• Page 8 line 10-11; please provide references</li> <li>• Please comment on the implications of your study. What does your finding mean to the public, scientific community and the current state of knowledge etc.</li> </ul>
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<b>REVIEWER</b>	Dr Mark Johnson University Hospital Southampton NHS Foundation Trust, Southampton, UK
<b>REVIEW RETURNED</b>	05-Dec-2019

<b>GENERAL COMMENTS</b>	This is an interesting and well written paper, which presents some findings which are relevant to clinicians and policy makers. The methods are appropriate, and it is good to see the use of growth modelling with SITAR to try and better understand the relationship between patterns of growth and demographic and socioeconomic factors. I agree with the authors that linear models are not adequate for this sort of analysis, so am pleased they have used SITAR. The discussion is concise and clear and discusses relevant limitations and related literature.
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	<p>I have only a few minor comments which might further improve the paper if addressed.</p> <ol style="list-style-type: none"> <li>1. In the abstract the authors refer to 'lasso regression' but this is an acronym/abbreviation and so should be expanded in the abstract, as this is confusing to those who are not aware of this method (myself included!). Furthermore, when describing the participants the authors state that there are "1412 participants from a randomized iron deficiency anemia preventive trial in healthy infants". This is perhaps not enough information for the reader to understand the population used here, as on reading the full manuscript, it seems that the actual intervention of the trial came at a timepoint beyond that which is considered by the present manuscript (the infants included in the paper appear to have been included before they were randomised and received intervention). This should perhaps be reworded to make it clearer, as on the face to it, it raises the concern that half these infants received additional iron, which I don't think was the case (and if it was the case, then the description in the methods section of the main manuscript needs to be amended to make it clearer at what point the infants were included).</li> <li>2. Some figures about the size of the population and data available are included in the methods, but I think these things should be included in the results (as the authors did not know these until they started to look at the data). Similarly, the data regarding BIC and the second step analysis (and associated figure) in the statistical methods section probably count as results too, and so should be moved to the result section. I think this might help the reader follow the results more easily, as in the result section, the authors start talking about the model used, but it is not clear which model this is.</li> <li>3. Following on from this in the results section, when discussing Weight trajectories (page 7 line 49 onwards) it is unclear which model was used from the table in Appendix 2 (same goes for the following sections on Length and weight-for-length). Generally all these results are a little confusing at first, and whilst I get what has been done and what the relevant findings were, this was hard work and difficult to follow at times. The results section would benefit from being a little clearer and easier to follow in terms of the models chosen and what the findings mean in real terms.</li> </ol>
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## VERSION 1 – AUTHOR RESPONSE

Response to reviewer 1:

Thank you for your thoughtful review of our paper. Please find our responses to your comments below.

### Abstract

1. *Objectives: Replace "early life environment factors" with "sociodemographic factors"*  
We replaced the expression.
2. *Results: The first three lines of results should be method.*  
We moved these lines to methods.
3. *Results: Were education and SEP examined as separate covariate? Education is usually used as a proxy for SEP. Good to clarify how different are education and SEP in your study.*

We discuss the SEP and education measures in the second paragraph of the 'outcome and sociodemographic measures' subsection of the 'Methods' section.

4. *Results: Did you account for infant feeding or other maternal factors such as maternal body weight status, smoking in your analysis?*

We did not include either smoking or maternal body weight in our analyses. We discuss infant feeding and maternal smoking in the discussion section.

5. *Results: You presented results on velocity and growth timing, what about results for size?*

We have added a sentence in the abstract results section mentioning weight trajectory parameters.

6. *Results: In line with your aim, results on gestational age, maternal age and education should be presented as well.*

We have a word limit of 300 words for the abstract so we selected the most salient findings. Unfortunately, we cannot add findings regarding maternal age and GA. However, our findings regarding these exposures is in the results section.

7. *Conclusions: Please be specific about how the findings of your study would inform prevention efforts aimed at infant growth.*

As this is the first finding with this level of detail, we encourage replication of the results prior to specific recommendations for interventions.

Strengths and limitations of the study:

8. *Strengths and limitations of the study: I don't think the monthly measurement of anthropometrics in the first five postnatal months is a strength. Instead, it should be a limitation as other infant growth studies have much longer follow-up into childhood or adolescence.*

We have added a sentence to explain why we think the selection of this period to examine growth is a strength. This period is unique in its growth pattern and no study to date has presented an analysis of monthly measures within this period.

9. *Strengths and limitations of the study: Please provide some details as to what you meant by detailed measure of SEP. What SEP measure was used and why it is better.*

- a. We have added a sentence that clarifies why this index is an advantage to this study.

## Introduction

10. *Please comment more on why looking at the relationship between SEP and earliest period of infant growth is important. Extensive studies look at correlates of growth from infancy to childhood/adolescence and this studies would provide a broader picture on the research question, why these studies do not suffice. Stronger rationale for examining earliest period of infant growth is needed.*

In the second paragraph of the introduction we have added a sentence clarifying why study of this period is important. In addition to our rationale that this period of growth has not been studied very much, we also highlighted the unique nature of this growth and its capacity to have different associations with exposures than other periods.

11. *Provide some context as to why you hypothesize that SEP will be inversely associated with weight gain and positively associated with length gain. In low and middle income countries, this might not be the case, for example, higher SEP may be linked with higher weight gain.*

We have modified a sentence in the last paragraph of the introduction clarifying the context of the specific aim we described. The literature we cite does include middle-income countries.

## Methods

12. *Was total years of education included as part of Graffar index?*

We provide a detailed summary of the index in Appendix A1. Years of education for household head is included in the scale.

13. *Please clarify what do multiple comparisons mean?*

In the second to last paragraph of the methods, we have added more detail to the sentence describing multiple comparisons.

## Results

14. *Exclusion of pre-term infants does not fit with the rest of sentence describing the cohort. The exclusion should be mentioned in the methods and in results when describing the final sample size being included in the analysis before description of cohort characteristics.*

We removed reference to preterm infants in the results section and also added more detail to the study sample section in the methods section.

15. *Weight trajectories: Results on maternal age from unadjusted model were reported. What about results from the adjusted model? For gestational age, results from adjusted model were reported, but not unadjusted. The reporting of results should follow a consistent manner, i.e. reporting unadjusted then adjusted, not picking out significant associations and report those. Where are the results for SEP and weight trajectories?*

We have streamlined the reporting of results and consistently reported adjusted results. We have also included information regarding SEP and weight trajectories.

16. *Length trajectories: 'In the pooled group': do you mean overall sample without stratification by sex?*

We have added an extra sentence in the third paragraph of 'Statistical analyses' section clarifying what the pooled analyses represent.

## Discussion

17. *The first paragraph, where are the results on maternal age and gestational age? Where are the summary of findings on weight trajectories? The summary of findings should directly answer your aim.*

We added a paragraph following the first paragraph in the discussion that contains information on results for the maternal age and GA exposures.

18. *Please provide more details on the mechanisms: how breastfeeding and maternal smoking influence infant growth. Did you explore maternal smoking status and breastfeeding in your analysis? If not, these should be mentioned as limitation.*

We did evaluate breastfeeding and that information is located in the methods section (last paragraph of statistical analyses section) and last paragraph of the results section. b) We did not evaluate smoking in this analysis, and have added a sentence in the discussion (paragraph starting with 'plausible biological mechanisms') regarding smoking.

19. *Page 8 line 5-8: Have you reported any results on SEP and weight trajectories? When compare with other studies, you need provide some details and references for those studies.*

We have now added a brief mention of the lack of findings for an association between SEP and weight trajectories in the first paragraph of the discussion.

20. *Page 8 line 10-11; please provide references*

- a. On page 8, lines 10-11, there is only a reference to table 2, no text.

21. *Please comment on the implications of your study. What does your finding mean to the public, scientific community and the current state of knowledge etc.*

- a. We believe we have done as thorough a job as possible to address the meanings of the findings. Considering these are the first type of analyses covering the first six months of development, we believe more research needs to be done prior to any statements regarding public health implications.

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Response to reviewer 2:

Thank you for your considerate and constructive review of our paper. Please find our responses to your comments below.

### **Abstract**

1. *In the abstract the authors refer to 'lasso regression' but this is an acronym/abbreviation and so should be expanded in the abstract, as this is confusing to those who are not aware of this method (myself included!).*

We have changed the abstract text referring to the lasso method.

### **Methods**

2. *Furthermore, when describing the participants the authors state that there are "1412 participants from a randomized iron deficiency anemia preventive trial in healthy infants". This is perhaps not enough information for the reader to understand the population used here, as on reading the full manuscript, it seems that the actual intervention of the trial came at a timepoint beyond that which is considered by the present manuscript (the infants included in the paper appear to have been included before they were randomised and received intervention). This should perhaps be reworded to make it clearer, as on the face to it, it raises the concern that half these infants received additional iron, which I don't think was the case (and if it was the case, then the description in the methods section of the main manuscript needs to be amended to make it clearer at what point the infants were included).*

I have added more information to this statement in the second paragraph of the methods section.

3. *Some figures about the size of the population and data available are included in the methods, but I think these things should be included in the results (as the authors did not know these until they started to look at the data).*

We moved the sentence regarding the final sample size to the first paragraph of the results section.

4. *Similarly, the data regarding BIC and the second step analysis (and associated figure) in the statistical methods section probably count as results too, and so should be moved to the result section. I think this might help the reader follow the results more easily, as in the result section, the authors start talking about the model used, but it is not clear which model this is.*

We have moved the section of text discussing the BIC to the space following the first paragraph in the results section. Also, each header for the outcome contains information on the selected models.

**Results**

5. *Following on from this in the results section, when discussing Weight trajectories (page 7 line 49 onwards) it is unclear which model was used from the table in Appendix 2 (same goes for the following sections on Length and weight-for-length). Generally all these results are a little confusing at first, and whilst I get what has been done and what the relevant findings were, this was hard work and difficult to follow at times. The results section would benefit from being a little clearer and easier to follow in terms of the models chosen and what the findings mean in real terms.*
  - a. We have updated the appendix table A2 to better mark the best performing models and added the BIC information in the results section so a reader can identify the model in appendix table A2. We have also restructured the text for each of the anthropometric outcomes.
  
6. *Generally all these results are a little confusing at first, and whilst I get what has been done and what the relevant findings were, this was hard work and difficult to follow at times. The results section would benefit from being a little clearer and easier to follow in terms of the models chosen and what the findings mean in real terms.*
  - a. I have followed the suggestion from reviewer #1 to report just adjusted analyses and I hope these changes improve the results section. As noted in item #5 above, we have also restructured the text for each of the anthropometric outcomes.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Miaobing Zheng Deakin University, Australia
<b>REVIEW RETURNED</b>	11-Feb-2020

<b>GENERAL COMMENTS</b>	<p>The authors have adequately addressed all reviewer comments raised.</p> <p>I only have a few minor comments to further improve the paper.</p> <p>Abstract/conclusion: it's better to replace infant growth with infant length growth</p> <p>Introduction/second paragraph: The third sentence needs references.</p> <p>Discussion</p> <p>1) First sentence: should "first six months" be "first five months"?</p> <p>2) The third paragraph starting with " Of three previous studies...": more details about study characteristics for individual cited studies should be mentioned to allow better comparison with findings of the present study. Why ref 12 found an inverse association as opposed to "a positive association"? Some explanation should be given.</p> <p>3) The next paragraph starting with "Several prior studies representing..." ref 7 found no relationship, but the in the previous paragraph, you indicated that ref 7,8,10 found a positive association. Please check for accuracy.</p>
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<b>REVIEWER</b>	Dr Mark Johnson
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	National Institute for Health Research Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK
<b>REVIEW RETURNED</b>	07-Feb-2020

<b>GENERAL COMMENTS</b>	I am happy that the authors have adequately dealt with the reviewers comments, and appreciate their efforts. The manuscript is much clearer and has beended improved by the changes
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## VERSION 2 – AUTHOR RESPONSE

Response to reviewer 1:

Thank you for your thoughtful review of our paper. Please find our responses to your comments below.

1. *Abstract/conclusion: it's better to replace infant growth with infant length growth*  
We changed the language as requested.
2. *Introduction/second paragraph: The third sentence needs references.*  
We have added references to this sentence.
3. *Discussion: First sentence: should "first six months" be "first five months"?*  
We have changed the wording from 'six months' to 'five months'.
4. *Discussion: The third paragraph starting with " Of three previous studies...": more details about study characteristics for individual cited studies should be mentioned to allow better comparison with findings of the present study. Why ref 12 found an inverse association as opposed to "a positive association"? Some explanation should be given.*  
These studies use different methods and cannot be directly compared to our results, which led us to only describing direction of association. For ref 12, we have added text to clarify the reason for the difference: the inverse association was for the unadjusted result and the near null association corresponded to and adjusted estimate. We also clarified the association given for ref 12.
5. *The next paragraph starting with "Several prior studies representing..." ref 7 found no relationship, but the in the previous paragraph, you indicated that ref 7,8,10 found a positive association. Please check for accuracy.*  
For ref 7, the authors found no evidence to support a relationship for the trajectories prior to 6 months, but they found a separate positive association for trajectories up to 5 years. We have noted those differences in our descriptions of these results.