PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A complementary feeding intervention on stunted Guatemalan children: A randomized controlled trial
AUTHORS	Martinez, Boris; Farley Webb, Meghan; Gonzalez, Ana; Douglas, Kate; Grazioso, Maria del Pilar; Rohloff, Peter

VERSION 1 – REVIEW

REVIEWER	Reviewer name Giulia Mandelli Institution and Country IRCCS-"Mario Negri" Institute for Pharmacological Research, Italy Competing interests None declared
REVIEW RETURNED	13-Nov-2017

GENERAL COMMENTS	The manuscript entitled "Effect of an individualized complementary feeding intervention on growth and dietary quality in stunted Guatemalan children: An individually randomized controlled trial." presents an interesting study of the impact of an intensive and individualized approach to complementary feeding education for caregivers on feeding practices and growth over usual care. 324 children 6-24 months old were randomized (161 to the intervention and 163 to usual care). The study duration was 6 months from enrollment. Results suggest the presence of an improvement in children's dietary quality. I congratulate the authors for their optimal planning and management of the trial. I find the manuscript to be generally well written and easy to follow. Nevertheless, I would like to submit the authors some questions and suggestions: 1. Some typos or number inconsistencies: a) Page 10, line 170: close the parenthesis opened at line 169 b) Page 12, line 193: there is an error in the WAZ confidence interval; I think that lower limit should be -0.02 c) Page 13, line 209: there is an error in the reported estimate of improvement in minimum meal frequency; I think that it should be 2% instead of 3% d) Page 13, line 213: close the parenthesis opened at line 212 e) Table S1: the absolute numbers of groups (N=296 and N=28) seem to disagree with the numbers in flow-chart (Figure 1) 2. Some doubts: a) Page 9, line 150: authors state that z-test is used for proportion. I would have expected a Chi-square or Fisher's test, instead. Can I have clarifications about that? b) Table 2: in some cases, the change is negative (WAZ and WLZ), both in interventional arm and in the control one. Does it mean that there is a worsening for these children? I would have expected an opposite change: are there some explanations?

	3. Some suggestions: a) Table 1: - I would suggest to the authors to add in the table the variable 'number of children under 5 years' - Why do the authors stratify the LAZ/HAZ for some covariates (gender and number of children <5 years) and the feeding indicators for others (maternal education)? Maybe p-values could clarify the reason of this choice? b) About the mixed model: - I suggest authors to explain better the issue of hierarchical linear model (mixed model) because I'm afraid that a non-expert reader might not understand it. - I think that it is necessary to show the full results of the mixed model (all variables with their coefficients, standard errors, …), at least in the online supplement. - Authors do not show any information about the goodness of fit of the built model, in term of both calibration and discrimination. Regarding discrimination, authors could show the Area Under the ROC Curve. Regarding calibration, authors could use the Hosmer-Lemeshow test and the 'calibration belt' method (Stat Med. 2014;33(14):2390-407 and Stat Med. 2016;35(5):709-20). c) I think that could be clearer write 'RR=1.22 (95%CI 1.10-1.35)' instead of 'improvement of 22% (95% CI 10%-35%)'; in particular in the abstract. In this way, it's easier for readers quickly understand the measure used (risk ratio, odds ratio, ecc…) d) Authors state at page 11 (line 176-179) that subjects lost to follow-up have a significantly different LAZ/HAZ/WLZ/WHZ at baseline. I think that this issue is worth of a comment in the discussion section: could it create a bias in the analysis, thus affecting the results?

REVIEWER	Reviewer name Ana Garces Institution and Country INCAP Guatemala Competing interests None
REVIEW RETURNED	17-Nov-2017

GENERAL COMMENTS	This is an interesting study and very well written manuscript. My comments are mainly in relation to the methods section and the discussion: - Methods: Although it is mentioned in the supplement, the manuscript would benefit from more detail regarding the anthropometry measurements in this section (if the study nurses were independent of those who implemented the intervention, supervision, equipment, etc). Also, more information in the manuscript regarding what the "usual" care and "intervention" consisted of. It is a little confusing to understand what the usual care is (in the end, was it really the government intervention or something different?). I am unsure if the program ended because of the fiscal scandal, or if this strategy was allready changing before this; authors might want to check the reference that they used for that, as I belive this was a MOH decision back in 2014/2015. What was novel about the intervention that might have improved feeding practices? Did CHW discuss results with the mothers and follow up ?

	More detail on the dietary methods would also be useful, for readers to gain more insight. And just one sentence on how to interpret the poverty score would be good. - Discussion: The results are quite interesting, especially since they are consistent with national context and other studies, with a novel point of view. I suggest consideration of emphasizng that the strategy was started sort of late in the stunting process; there are publications about this from the Chimaltenango area about stunting and complementary feeding that could help to frame your findings (Berngard SC, Berngard JB, Krebs NF, Garcés A, Miller LV, Westcott J, Wright LL, Kindem M, Hambidge KM. Newborn length predicts early infant linear growth retardation and disproportionately high weight gain in a low-income population. Early Hum Dev. 2013 Dec;89(12):967-72. PMID: 24083893 PMCID: PMC3859373) (Krebs NF, Mazariegos M, Chomba E, Sami N, Pasha O, Tshefu A, Carlo WA, Goldenberg RL, Bose CL, Wright LL, Koso-Thomas M, Goco N, Kindem M, McClure EM, Westcott J, Garces A, Lokangaka A, Manasyan A, Imenda E, Hartwell TD, Hambidge KM. Randomized controlled trial of meat compared with multimicronutrient-fortified cereal in infants and toddlers with high stunting rates in diverse settings. Am J Clin Nutr. 2012 Oct;96(4):840-7. PMID 22952176 PMCID: PMC3441111).

REVIEWER	Reviewer name Raul Mercer Institution and Country FLACSO (Latin American School of Social Sciences) Buenos Aires, Argentina Competing interests NO
REVIEW RETURNED	11-Dec-2017

GENERAL COMMENTS	The work is interesting and takes place in a population (Guatemala) historically traversed by structural poverty and social deprivation of indigenous groups (Mayans). For its part, Guatemala has been a field of experimentation and research on nutritional issues in childhood without the expected impact at the population level. The work is very well written and follows a logical sequence of contents and methodological aspects. The discussion is detailed on the justifications of some of the results obtained, including the contingencies associated with the study. Here, some observations to be clarified by the authors: What is the reason why the follow-up period of 6 months was established and not more? All this, considering that one of the reasons why the authors explain the lack of significant findings could be due to this cause. In the same way and on the basis of the critical 1000 days window, why was the intervention started after 15 months of age? What is the explanation for which only increased consumption of certain food groups such as legumes and Vitamin A and not others as the case of proteins was observed? (Supplementary Table 3). This comment is related to the recent studies on the use of eggs in early complementary feeding and child growth done in Ecuador.

	http://pediatrics.aappublications.org/content/early/2017/06/05/peds.2016-3459..info In relation to Incaparina, is it a culturally accepted complementary food? Was there evaluation of their consumption in children?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Comment: 1. Some typos or number inconsistencies:
a) Page 10, line 170: close the parenthesis opened at line 169
b) Page 12, line 193: there is an error in the WAZ confidence interval; I think that lower limit should be -0.02
c) Page 13, line 209: there is an error in the reported estimate of improvement in minimum meal frequency; I think that it should be 2% instead of 3%
d) Page 13, line 213: close the parenthesis opened at line 212

Response: Thanks for your detailed review on these inconsistencies, all of them had been checked and corrected.

Comment: e) Table S1: the absolute numbers of groups (N=296 and N=28) seem to disagree with the numbers in flow-chart (Figure 1)

Response: We apologies for these inconsistencies. We have clarified that 12 subjects were LTF in the control and 16 in the intervention arm. In addition, 3 additional subjects left the study, however exit data was available and were included in the intention-to-treat analysis. These corrections have been harmonized in the text and Figure 1 flow chart.

Comment: 2. Some doubts:
a) Page 9, line 150: authors state that z-test is used for proportion. I would have expected a Chi-square or Fisher's test, instead. Can I have clarifications about that?

Response:
The z-test for two independent proportions is mathematically identical to a 2x2 chi squared test (see, for example Wallis 2013, J Quant Ling, https://doi.org/10.1080/09296174.2013.830554).
We have changed the text in the manuscript to read chi squared, since as the Reviewer points out, this test will be more familiar to most readers of the journal.

Comment: b) Table 2: in some cases, the change is negative (WAZ and WLZ), both in interventional arm and in the control one. Does it mean that there is a worsening for these children? I would have expected an opposite change: are there some explanations?

Response: Yes, in rural Guatemala, children are typically very vulnerable and at high risk for growth faltering. The natural growth history in this population is gradual subtle decline in weight-based indicators and more dramatic decline in height-based indicators throughout the first two years of life.

Comment: a) Table 1:
- I would suggest to the authors to add in the table the variable 'number of children under 5 years'
- Why do the authors stratify the LAZ/HAZ for some covariates (gender and number of children <5 years) and the feeding indicators for others (maternal education)?
Maybe p-values could clarify the reason of this choice?

Response: - We have added the indicator variable “children under 5 years to table 1. This is a great suggestion.

- We agree that our stratification by covariates was not well explained. In the methods section, we note that our prespecified statistical analysis plan included bivariate analysis of outcomes for certain covariates. Where those covariates where significant ($p<0.05$) we have stratified outcomes in the table. We add p-values for these covariates to the first paragraph of the results section (Subject enrollment and baseline characteristics) to further clarify this point.

Comment: b) About the mixed model:

- I suggest authors to explain better the issue of hierarchical linear model (mixed model) because I'm afraid that a non-expert reader might not understand it.
- I think that it is necessary to show the full results of the mixed model (all variables with their coefficients, standard errors, …), at least in the online supplement.
- Authors do not show any information about the goodness of fit of the built model, in term of both calibration and discrimination. Regarding discrimination, authors could show the Area Under the ROC Curve. Regarding calibration, authors could use the Hosmer-Lemeshow test and the ‘calibration belt’ method (Stat Med. 2014;33(14):2390-407 and Stat Med. 2016;35(5):709-20).

Response: We have added additional text to the methods section describing our rational for use of the mixed model and our approach. We also include a new reference to an excellent Mixed Models text that we have followed closely in applying our model.

We have included the full statistical output for the final mixed model in the online supplement.

For reporting the performance of linear mixed model, in the methods text we now mention that the final model presented in the paper was produced from the fully specified model by removing nonsignificant fixed effects through serial likelihood ratio tests.

In addition, we report in the results section the chibar2 statistic and p value (Breusch-Pagan Lagrange multiplier test), which is the primary test for showing that the linearl mixed model outperforms the simple linear regression.

The Hosmer Lemeshow test mentioned by the reviewer is specific for logistic (not linear) regression, and so we do not report that here.

Comment: c) I think that could be clearer write ‘RR=1.22 (95%CI 1.10-1.35)’ instead of ‘improvement of 22% (95% CI 10%-35%)’; in particular in the abstract. In this way, it’s easier for readers quickly understand the measure used (risk ratio, odds ratio, ecc…)

Response: We have changed the abstract’s text to include the RR
Comment: d) Authors state at page 11 (line 176-179) that subjects lost to follow-up have a significantly different LAZ/HAZ/WLZ/WHZ at baseline. I think that this issue is worth of a comment in the discussion section: could it create a bias in the analysis, thus affecting the results?

Response: A comment about possible added bias has been included the discussion.

Reviewer 2
Comment: - Methods: Although it is mentioned in the supplement, the manuscript would benefit from more detail regarding the anthropometry measurements in this section (if the study nurses were independent of those who implemented the intervention, supervision, equipment, etc).

Response: We have added back some requested elements from the Supplementary File to the main text, while trying to still remain cognizant of overall manuscript length.

Comment: Also, more information in the manuscript regarding what the "usual" care and "intervention" consisted of. It is a little confusing to understand what the usual care is (in the end, was it really the government intervention or something different?).

Response: We defer to the Editors on whether these additions to manuscript length remain acceptable.

The usual care intervention consisted of the Zero Hunger Plan scheme, however implemented by CHW staff from the NGO, given closure of the government program early in the preparatory stage of our trial. We have added a few additional details about the intervention from the supplement to the main manuscript, however many of the details we again have left in the supplement given concerns about overall manuscript length.

Comment: I am unsure if the program ended because of the fiscal scandal, or if this strategy was allready changing before this; authors might want to check the reference that they used for that, as I belive this was a MOH decision back in 2014/2015.

Response: We have corrected the sentence and cited Avila et al. as reference. This was a great observation.

Comment: What was novel about the intervention that might have improved feeding practices? Did CHW discuss results with the mothers and follow up ?

Response: The main hypothesis of the study is that an individualized approach to feeding education (guided by an assessment of the individual child's feeding data, as opposed to the standard approach which involves use of generic age-based feeding recommendations which are given to all children) is more effective.

The unique element of the intervention arm is, therefore, the formal individualization of the home visit (dietary recall) and education (education tailored to the findings from the recall). A few additional sentences in the Methods section, added back at the Reviewer's suggestion from the Supplemental File, help to make this point more clearly.

Comment: More detail on the dietary methods would also be useful, for readers to gain more insight.

Response: This is a good point. These WHO indicators have now made it into national DHS surveys but are still not commonly and widely used by all practitioners. To address this, we have included a table in the Supplementary File with definitions of the feeding practices indicators used as dietary methods in our study, and reference this Table in the Methods section

Comment: And just one sentence on how to interpret the poverty score would be good.

Response: The poverty score references a look-up table for likelihood of living below the poverty line. This is not the most intuitive scale, therefore (since it gives a likelihood score). Therefore, we have provided, as a point of reference two examples of the interpretation of the likelihood of living in poverty based on the family poverty score in the Methods section.

Comment: - Discussion: The results are quite interesting, especially since they are consistent with national context and other studies, with a novel point of view.

I suggest consideration of emphasizng that the strategy was started sort of late in the stunting process; there are publications about this from the Chimaltenango area about stunting and complementary feeding that could help to frame your findings (Berngard SC, Berngard JB, Krebs NF, Garcés A, Miller LV, Westcott J, Wright LL, Kindem M, Hambidge KM. Newborn length predicts early infant linear growth retardation and disproportionately high weight gain in a low-income population. Early Hum Dev. 2013 Dec;89(12):967-72. PMID: 24083893 PMCID: PMC3859373) (Krebs NF, Mazariegos M, Chomba E, Sami N, Pasha O, Tshefu A, Carlo WA, Goldenberg RL, Bose CL, Wright LL, Koso-Thomas M, Goco N, Kindem M, McClure EM, Westcott J, Garces A, Lokangaka A, Manasyan A, Imenda E, Hartwell TD, Hambidge KM. Randomized controlled trial of meat compared with multimicronutrient-fortified cereal in infants and toddlers with high stunting rates in diverse settings. Am J Clin Nutr. 2012 Oct;96(4):840-7. PMID 22952176 PMCID: PMC3441111).
Response: We definitely agree with this insight. Given that this was a complementary feeding intervention, we could not start earlier than 6 months of age, and given the increasing prevalence of stunting over two years, proportionately older children were enrolled. We mention these considerations now in the Discussion, and we also include citations to the suggested references.

Reviewer 3

Comment: What is the reason why the follow-up period of 6 months was established and not more? All this, considering that one of the reasons why the authors explain the lack of significant findings could be due to this cause.

Response: Under Study Context in the Methods we mention that the study was conducted in collaboration with a local partner, whose existing nutrition program provided the programmatic framework for the design of our intervention. Since this program's approach consists of a 6-month-long complementary feeding education intervention, the 6 month window represented a pragmatic limit on the length of our intervention.

In the Discussion, we have clarified and emphasized this short intervention period of 6 months as a possible explanation to our non-significant changes in linear growth.

Comment: In the same way and on the basis of the critical 1000 days window, why was the intervention started after 15 months of age?

Response: This is an important point. Please see response above to Reviewer 2's final point.

The intervention was not started at 15 month of age, rather it was open to all children within the critical window where complementary feeding was appropriate (6-24 months). However, the mean age of enrolled children was 15 months, including younger and older children.

Comment: What is the explanation for which only increased consumption of certain food groups such as legumes and Vitamin A and not others as the case of proteins was observed? (Supplementary Table 3). This comment is related to the recent studies on the use of eggs in early complementary feeding and child growth done in Ecuador.
http://pediatrics.aappublications.org/content/early/2017/06/05/peds.2016-3459..info

Response: We observed a near significant consumption of eggs (lower bound of CI at 1.00) which were part of the intervention, and we've modified the text to mention this and also include the recommendation citation.

Other food groups (especially flesh foods and dairy) did not improve, and this is expected because they are expensive and not part of the local diet.

We anticipate improvement in food groups in the ration and in those which are locally grown (e.g fruits/vegetables) which is what we were able to observe here. We've added this clarification to the discussion section.

Comment: In relation to Incaparina, is it a culturally accepted complementary food? Was there evaluation of their consumption in children?

Response: Incaparina is a very common complementary food supplement in Guatemala, which has been around for decades. We include a clarifying line in the Supplementary File now to emphasize this.

The 24-h dietary recall used in the study was modelled after the WHO's tool, and it is designed to count food groups and daily meals. It does not, however, permit formal quantification of individual foods, however. This limitation of the study is mentioned in the Discussion.

VERSION 2 – REVIEW

REVIEWER	Reviewer name Giulia Mandelli Institution and Country IRCCS -"Mario Negri" Institute for Pharmacological Research Italy Competing interests None declared
REVIEW RETURNED	08-Mar-2018

GENERAL COMMENTS	Thank you for properly addressing the comments. I have no other suggestions.