Author's response to reviews

Title: Determinants of rapid weight gain during infancy: baseline results from the NOURISH randomised controlled trial.

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Version: 2 Date: 13 July 2011

Author's response to reviews: see over
4 July 2011
To the Editor
BMC Pediatrics

Dear Editor,

We thank the reviewers for their helpful comments on our paper. We have made the changes as outlined below and also attach a copy of the revised manuscript. We now believe that the paper has been improved significantly.

With regard to the editors comments the trial registration number has been added at the end of the abstract.

Below we have given a point by point response to the reviewers comments:

Reviewer's report
Title: Determinants of rapid weight gain during infancy in participants in the NOURISH early feeding trial.
Version: 1 Date: 20 March 2011
Reviewer: Mandy Belfort

Reviewer's report:
These authors address an important scientific question regarding the potentially modifiable risk factors for rapid infant weight gain. They use an appropriate dataset to examine this question, and specifically focus on feeding practices and behaviors. I do have several critiques and suggestions for the authors, as listed here.
1. Is the question posed by the authors well defined? Yes
2. Are the methods appropriate and well described? Here I list concerns regarding the methods as currently described.
2a. This appears to be a cross sectional analysis, that is, the assessment of feeding practices (the exposure) occurs at the same time as the assessment of the infant’s weight, which reflects the weight gained from birth (the outcome). The authors should clarify that this is a cross sectional study.

We understand the reviewers concerns and have now rewritten the methods to reflect the fact that the data are in fact baseline results from a randomised controlled trial (prospective longitudinal intervention study). This is not a cross sectional analysis. Our outcome variable is a difference in weight-for-age Z-score between birth and baseline assessment and therefore represents data from two time points and a change function which cannot be obtained from a cross sectional analysis. Similarly for our exposure variables we have collected data from two points: firstly, from the point of recruitment in the postnatal ward, where consenting mothers supplied some demographic and birth information and secondly, information at the baseline assessment when infant feeding practices and styles are measured at 4-7 months of age and some further demographic data was collected. This prospective study will continue until the children are at least 2 years of age. A recent article describing ethnic differences in early weight gain with an analysis plan almost identical to ours (see de Hoog ML et al. The role of infant feeding practices in the
2b. *It is not clear to me how feeding type was categorized.* When the authors write “breastfeeding,” do they mean feeding at the breast, or feeding breast milk (at the breast or from a bottle)? Similarly, does “combination feeding” mean breast milk and formula, or feeding at the breast and from a bottle (which could be expressed breast milk). These are key distinctions given the authors’ hypotheses regarding behaviors around feeding from bottle vs. at the breast with respect to self-regulation and satiety.

The section on feeding type has been rewritten with subheadings. Breastfeeding meaning breastmilk only, combination feeding meaning both breastmilk and formula etc. No data was collected on mode of feeding, (that is if child was fed by bottle or by breast eg. expressed breastmilk fed by bottle), which is indeed important for our hypothesis and this has now been stated as a limitation in the discussion section.

2c. *Why did the authors combine all the breastfeeding categories and compare with formula only? Would be interesting to see if there is a “dose response” across categories.*

Our aim in this study was to determine which modifiable factors were associated with excessive early weight gain. In previous studies formula feeding and feeding on schedule have been shown to be associated and therefore we examined formula feeding and feeding on schedule as risk factors for early weight gain. We have also shown some further analysis that we conducted below (see output below) and although there does indeed seem to be a dose response effect across categories with a lower proportion of exclusively breastfed infants categorised as rapid growers, followed by combination fed infants in comparison to formula fed infants, there is no statistically significant effect (Chi square for trend P value = 0.224) and this was probably due to the small sample size in each group. We have chosen to use formula feeding and feeding to schedule as risk factors so have combined categories to look at these variables as risk factors, and we stated this in the methods section.

<table>
<thead>
<tr>
<th>diffZscore &gt; 0.67 * Newfeed1 Crosstabulation</th>
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<tr>
<td>Newfeed1</td>
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<tr>
<td>diffZscore &gt; 0.67 Yes Count</td>
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<tr>
<td>% within Newfeed1</td>
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<tr>
<td>No Count</td>
</tr>
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<tr>
<td>Total Count</td>
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<tr>
<td>% within Newfeed1</td>
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</table>
2d. Did the authors administer only those 2 questions from the Infant Feeding Practices Questionnaire? If they administered more than the 2, they should report all the relevant questions asked (even if results are null).

We administered all the questions from the IFPQ but the data from the full questionnaire have not yet been analysed. The other questions in this questionnaire are not central to the hypothesis for our analysis (i.e., that feeding on schedule is associated with excessive early weight gain) and we also intend to publish further data from the IFPQ in a descriptive analysis which focuses on the behavioural aspects of feeding (e.g., fussiness etc) as distinct from feeding styles.

2e. Why did they authors combine “on demand” and “mixed” feeding styles? Again would be interesting to evaluate potential “dose response” across >2 categories.

As stated above with feeding types we intended to look at feeding on schedule as a risk factor for early weight gain. Although again there seems to be a dose response effect across categories with a greater proportion of children fed on schedule being categorised as rapid growers than the on demand or mixed groups (see below), there is no statistically significant effect and we chose to combine categories enabling the multivariable comparisons of feeding on schedule as a risk factor for excessive early weight gain, consistent with a similar position for formula feeding.

<table>
<thead>
<tr>
<th>diffZscore &gt; 0.67 * Demand/Schedule/Combination Crosstabulation</th>
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<tbody>
<tr>
<td><strong>Demand/Schedule/Combination</strong></td>
</tr>
<tr>
<td>on demand</td>
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<tr>
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<tr>
<td>no</td>
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<tr>
<td>diffZscore &gt; 0.67</td>
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<td>% within Demand/Schedule/Combination</td>
</tr>
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<td>% within Demand/Schedule/Combination</td>
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<tr>
<td>diffZscore &gt; 0.67</td>
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<tr>
<td>% within Demand/Schedule/Combination</td>
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</table>

3. Are the data sound?
3a. Please clarify how the sample was derived. How many eligible? How many provided data in newborn period? How many provided data at follow up? How many excluded due to missing data? These seem more relevant to this analysis than whether participants ultimately enrolled in the trial.
We have added the following sentence describing how the sample was derived “At the first postnatal contact 2169 women agreed to subsequent contact for enrolment in the trial and provided relevant details. Subsequently we were unable to contact 511, 74 became ineligible, 885 declined consent and the remaining 698 provided signed consent and underwent baseline assessment followed by randomisation.”. Table 1 shows a comparison of the women that provided complete data (N=612) and those who had data missing (n=86).

3b. In the descriptive results of feeding practices, the categories for breast and formula feeding should identical to how described in the methods section. We have rewritten this section and now the categories for breastfeeding and formula feeding are identical to the methods section.

3c. Suggest highlighting that participants’ mean weight-for-length z score was -0.28, suggesting that overall infants were ~1/3 SD thinner than the WHO Standard. We have added a sentence stating this in the results section.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes
6. Are limitations of the work clearly stated? The authors do state some limitations but I think they also need to emphasize the cross sectional nature of the study. An additional limitation is that they assessed weight gain, rather than gain in weight-for-length which reflects adiposity better and may be more relevant to later obesity. Birth length was not collected in our study so we were unable to measure differences in weight-for-length between birth and baseline assessment. This measure, as the reviewer states, may reflect adiposity better and this point has been added to the limitations section in the discussion.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? Yes

Discretionary revisions:
- p. 5, Background, 2nd para regarding definition of overweight/obesity could be omitted, as not relevant to outcome of this study (rapid infant weight gain) We prefer not to omit this paragraph because it is central to our argument that rapid weight gain in infancy is an important predictor of overweight and obesity – it is therefore important how both rapid weight gain and overweight/ obesity is defined. Reviewer 2 has suggested that we add a sentence regarding why the WHO standards were used and we have added this and this may link the paragraph better to this study.

- p. 4, Background, 1st para, 3rd sent, birth weight does not truly influence weight gain, rather is (inversely) associated with it, suggest rewording. We have reworded this as the reviewer has suggested.
- Consider adding table with prevalence of responses to infant feeding questions
As stated above we have only analysed data that are central to our hypothesis. This is a baseline analysis of a prospective study and a fuller analysis of the behavioural aspects of feeding will be submitted in a separate report focused on behavioural processes in relation to outcomes.

- Consider highlighting that participants’ mean weight-for-length z score was -0.28, suggesting that overall infants were ~1/3 SD thinner than the WHO Standard
We have added this section to the results section under growth parameters and change in weight.

Minor essential revisions:
- p. 6, Methods, Study design and participants, please clarify how the sample was derived (see 3a above)
We have added a short sentence about this to the methods section.

- p. 6, Methods, Study design and participants, term is #37 weeks, not >35 weeks
We have corrected this.

- p. 7, Methods, Data collection, last sentence, should be “weight-for-height” not “height-for-weight”
We have corrected this to weight-for-length.

- p. 9, Methods, Outcome variables, please clarify what is meant by “…tracking above weight percentiles”
We agree with the reviewer that this is confusing and have replaced this “crossing centile bands on a growth chart” as it was described in the abstract.

- p. 9, Methods, Statistical analyses, please clarify what is meant by “…in a contextual sense” regarding differences between included and excluded participants
Since both reviewers required clarification here we have now refer to a statistically significant difference between those who remained in and those who dropped out of the study.

- p. 10, Results, Feeding practices and styles, categories should be identical to Methods section
We have altered this as requested.

- p. 12, Discussion, sentence starting with “Formula feeding has been…,”add “excessive” before “early weight gain”
We have added ‘excessive’ before early weight gain.

Major essential revisions:
- Please clarify that this is a cross sectional study, both in the methods and in the Discussion sections (see 2a and 6 above).
We do not agree that this is a cross sectional analysis for the reasons discussed above (see point 2a) but we have been more specific in defining this as a prospective longitudinal intervention study.

- Please clarify how feeding type was categorized (see 2b above)
  We have clarified this in the text (please see above).

- If feasible, please analyze feeding type and style across >2 categories (see 2c and 2e above)
  We have addressed this point above.

- Please address comment re: other questions from the Infant Feeding Questionnaire were asked (see 2d above)
  We have addressed this above.

- Please address additional limitation in Discussion section (see 6 above)
  This has been added to the limitation section in the discussion.

**Level of interest:** An article whose findings are important to those with closely related research interests  
**Quality of written English:** Acceptable  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.  
**Declaration of competing interests:**  
I declare I have no competing interests

Thank you for considering our submission and we look forward to your response.

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**Reviewer's report**  
**Title:** Determinants of rapid weight gain during infancy in participants in the NOURISH early feeding trial.  
**Version:** 1  
**Date:** 16 May 2011  
**Reviewer:** Jackie Blissett

**Reviewer's report:**
This is an interesting study in the very valuable subject area of rapid infant weight gain that should be of interest to many readers of BMC Pediatrics. The authors examine the predictors of rapid weight gain from birth to 4-7 months of age, based on baseline data from a cohort of infants who are part of a large RCT examining an intervention to promote positive feeding practices. The study has some important findings, but I also have some concerns about a number of aspects of the design and interpretation.

- **Major Compulsory Revisions**
  The author must respond to these before a decision on publication can be reached. For example, additional necessary experiments or controls, statistical mistakes, errors in interpretation.
  1. My primary concern with this paper is that it is a report on baseline data from an RCT prior to randomisation and administration of intervention, but that it is not clear from the outset that the paper does not report the outcomes of the RCT nor make use of other data from the RCT, of which the methods are described. For example, methods paragraph 5 describes a questionnaire concerning food
refusal, fussiness, restrictive feeding, parenting skills but the data are not reported and these measures are not mentioned again in the paper, which may be misleading or confusing for readers. I do not object to the use of these data to investigate an important question, and it has to be acknowledged that the participants came from a trial, but I think the framing of the paper, from title, through abstract and method, needs to be clearly linked to ONLY the focus of the research in question, not the trial more generally.

We agree with this criticism and thank the reviewer for pointing this out. We have made some substantial changes to the text to reflect this and reframed the paper. The changes include:

1. Changing the title to specify that this represents a baseline analysis
2. Abstract and methods have been rewritten to be clearer about the fact that these are baseline results from an RCT.
3. We have been more specific about the questions that were used for the analysis from the infant feeding practices questionnaire.
4. We have clearly stated the aims of this analysis in the background section and the fact that we have used baseline results from the RCT.
5. In the conclusions we have highlighted the fact that further results of NOURISH including outcomes of the intervention itself will be forthcoming.

2. Method paragraph 6 exposure variables: groups were clustered into formula feeding and any breastfeeding. Do the authors have any data on the types of breastfeeding strategies they could present here e.g. proportion of feeds that are breast milk, expressed breast milk etc? This matters, given that someone who is mixed feeding could formula feed for the majority of the time, and express breast milk to be given in a bottle for the remaining minority of the time. This does change the dynamic of the feeding interaction and has implications for your conclusions about the mechanism of any protective effects of breastfeeding (or detrimental effects of formula feeding). Did the authors consider ‘removing’ the mixed feeding cases? Would analyses be substantially different if one compared ‘pure’ breastfeeding to formula feeding? A similar comment may be made about the division of feeding to schedule and mixed feeding style.

We do not feel it is statistically appropriate in the actual report to remove the mixed feeding and combination feeding cases. In both analyses this would have reduced our sample size to almost half. We can provide the reviewer with the tables below which show that although the differences may be important and clinically relevant, in both comparisons it is not statistically significant (P>0.05). We can also refer the reviewer to our response to Reviewer 1 (three group comparisons).

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<th>Total</th>
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</tbody>
</table>
- Minor Essential Revisions

3. The authors need to explain why there is such variation in timing of baseline data collection. This is a weakness of the study, given that baseline data collection is therefore occurring at a period in which solid feeding is likely to commence. Whilst the study does attempt to examine this as a factor, and controls for age of infant in the models, I think it is important to explain the reasons for this variations and to include in the discussion how this may limit the study. It would be useful to know, for example, whether the age at which baseline data were collected was related to the speed of weight gain, or whether it differentiated between rapid and slower weight gain groups.

The main reason for the variations in the age at baseline assessment is because some women were not able to return questionnaires and come in for the baseline assessment sooner, mainly for logistic reasons. When recruiting participants for this long term study we felt it necessary to be flexible as they were all first time mothers who may have been overwhelmed with a strict schedule and therefore more likely to withdraw from the study. Our purpose was to have them commence the intervention before 6 months and most of them did this (only 4 infants were over 6 months of age). As the reviewer correctly points out we have also adjusted for age in our analyses. We agree with the reviewer that this range of ages is a weakness and have added a sentence about this to the discussion of limitations section.

4. Method paragraph 5 under data collection: it is stated that ‘prior to the baseline assessment’ a series of measures were given. As previously discussed this needs to clearly delineate which are going to be reported on in the current study, and needs to explain more precisely when these measures were given. This paragraph also refers to a growth assessment in the last line. Is this the same as the baseline assessment?

The methods have been rewritten and we have been more specific about when the measures have been taken. We have changed growth assessment to ‘baseline’ assessment to be more consistent with our descriptions.

5. Discussion paragraph two focuses on the fact that the study supports the idea that behavioural factors such as a maternal control of feeding may be important mechanisms. However, there is nothing in the study that negates the role of the bioactive components of breast milk (e.g. leptin) or the constituents of breast milk (lower calorie and lower protein). In other words, especially given that the methods of mixed feeding are not taken into account, one might argue that the study gives evidence for the potential role of bioactive aspects of breast milk, as well as the behavioural advantages of breastfeeding for self regulation. This needs to be considered.

We agree with the reviewer and a sentence on the importance of content of breastmilk has been added to paragraph 2 of the discussion.

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<table>
<thead>
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<th>Count</th>
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<td>100.0%</td>
<td>100.0%</td>
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</tbody>
</table>
- Discretionary Revisions
6 Background paragraph 2 I felt the sentence which describes the relationship between increased length of breastfeeding and weight gain could be rephrased to explain whether ‘in the 3-6 month group’ refers to the relationship being strongest in this age group, OR that the relationship is stronger in groups breastfed to this age.
This has been rephrased to “where the relationship was strongest when infants were aged from 3 to 6 months”.

7 Background paragraph 2 also describes the studies which have and have not found a link between breastfeeding and BMI. I wondered if it might be useful to highlight that where positive relationships are not found, the literature usually finds null effects rather than inverse effects and that this may be an issue of power for many of the studies.
We have included this statement in the background section “In studies where a positive relationship was not found there is usually no effect rather than inverse effects and this may be because most of them lacked statistical power to detect an association”.

8 Background paragraph 4 explains the WHO growth standards. It might be useful to explain why these particular standards were chosen as the reference for this group of infants.
A statement about the appropriateness of the WHO growth standards has been added to the background section.

9. Statistical analyses paragraph 1: ‘compared qualitatively to determine if there were substantial differences in a contextual sense’- this did not make clear sense to me, and it was not reported whether there were any substantial differences between groups as a result of this process.
As both reviewers have commented on this, we have rephrased this section, the differences have been highlighted in greater detail and we have included p values.

10. Results: feeding practices and styles: 32.5% of infants had started solids. However, given that some of them were over 6 months old, this is not surprising. It would be better to report the percentage of people introducing solids before national/international guidelines recommend.
We have added a sentence after this stating that of the children who had started solids aged 24% had introduced solids before 4 months of age.

Once again we would like to thank the reviewers for their helpful suggestions and we now believe the article has been improved significantly. We look forward to hearing from you soon.

Yours sincerely
Seema Mihrshahi
Postdoctoral Research Fellow
Queensland University of Technology