Author’s response to reviews

Title: Socioeconomic differences in childhood length/height trajectories in a middle-income country: a cohort study

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Author’s response to reviews: see over
Dear Dr. Popham,

Re: MS: 7566031481160034 - Socioeconomic differences in childhood length/height trajectories in a middle-income country: a cohort study

Thank you for your e-mail dated 21 April 2014 inviting us to respond to Reviewers’ comments. We have considered these comments carefully and our responses and amendments to the manuscript are reported below. All additions to the manuscript are underlined and all deletions crossed-through, for ease of cross-referencing our responses to the Reviewers’ comments.

Reviewer's report 1
Reviewer: Barbara Lourenco

**General comments:** This is a nicely written manuscript that prospectively accesses the influence of socioeconomic status on length/height gain in a large sample of children through 7 years of age in a middle-income setting. Aims were well defined, methods seem appropriate in general and I believe the study may contribute for expanding public health knowledge in its field with a solid body of data. Some clarification is though necessary to make the manuscript more concise, as depicted in the observations and suggestions below.

**Response:** Thank you for these positive comments. We have addressed your suggestions below.

**Major compulsory revisions:**
1. Background, first paragraph: I do not fully agree with the rationale presented in the last sentences – some of the studies cited by the authors in fact contributed for advancing knowledge about at what age socioeconomic differences in length/height emerge, if these differences are modified with age during childhood, and possible mechanisms (these points would not be, therefore, completely “unclear” to date). I believe it would be important to reformulate these statements and thus clarify throughout the introduction section how the present study contributes to the literature in the field. Please also adapt the background in the abstract of the manuscript accordingly.

**Response:** This is an important point; we have removed the last sentences and added the following sentences.

*Abstract:*

**Background:** Socioeconomic disadvantage is associated with shorter adult stature. Short stature is associated with higher risk of cardiovascular disease and overall mortality. Few studies have examined
the development of socioeconomic differences in stature by examining the growth trajectory from birth to childhood and the mechanisms involved, particularly in a middle-income former Soviet setting.

Background:
Adult attained height reflects fetal, infant and childhood growth and hence the influence of in utero and postpartum environment and genes [1, 2]. Height is an important marker of health, because shorter people have higher cardiovascular disease risk [3, 4] and higher overall mortality [5], albeit a lower risk of developing some cancers [4-6]. Socioeconomic differences in length and/or height (abbreviated to length/height) have been demonstrated at all ages and in various settings [7-14], with socioeconomic disadvantage associated with shorter stature.

Few studies have examined the development of socioeconomic differences in length/height from birth through infancy to childhood using repeated measures of stature; of those that have, most have been set in high-income countries [23-26], with fewer in low- or middle-income countries, such as Brazil [18, 27] or former Soviet countries, such as Russia [28]. It is important to understand not only the magnitude and timing of the emergence of socioeconomic differences in length/height (as these may clarify important growth periods when public health interventions aimed at reducing these differences, and hence inequalities in later health outcomes, might be targeted), but also the mechanisms involved (which may suggest modifiable factors suitable for intervention). By examining socioeconomic differences in childhood growth and the factors that affect growth in a middle-income former Soviet country, we aimed to understand whether the findings are specific to this context or share similarities with those in other settings.

Discussion:
In summary, despite low reported levels of income inequality [30], socioeconomic differences in length/height growth amongst children from Belarus were present at birth and widened through early infancy and early childhood. These differences were partly explained by mid-parental height, suggesting that factors influencing the parents’ growth during their own childhood have a bearing on these socioeconomic differences. Our findings suggest that public health interventions aimed at improving socioeconomic conditions in early childhood might help reduce socioeconomic differences in length/height in this setting.

2. Methods, statistical methods, first paragraph: please clarify why the knots at 3, 12, and 34 months were chosen to model the growth trajectories.

Response: We have added a description of how the knots were chosen to model the growth trajectory:

Methods:
Length/height growth velocity was predicted for each child by a linear spline multilevel model with 3 knots at 3, 12 and 34 months, the knots were chosen that best fitted the data. Full details of the model selection process have been published elsewhere [37, 38]. The knot points generated four splines, estimating different length/height growth rates between 0-3 months, 3-12 months, 12-34 months and 34-84 months; designated as 'early infancy', 'late infancy', 'early childhood' and 'late childhood', respectively. The model assumes piecewise linear growth and is therefore a simplification of the underlying growth process. Although a linear spline model is an approximation of the true growth function; its coefficients are easily interpretable and have been shown to produce good model fit in this and several other cohorts [18, 23, 37-40]. Furthermore, analyses in four other cohorts in different settings have resulted in similar knot points, providing some face validity that the growth periods
identified represent meaningful distinct periods of growth that are similar across children from different ethnic and socioeconomic backgrounds \[18, 23, 37-40\]. Individual- and occasion-level residuals were approximately normally distributed. Our approach assumes that residuals are uncorrelated and that any missing outcome data are missing at random. However, even if the autocorrelation assumption is violated, the fixed effects, which we report, are likely to be unbiased \[41\]. The advantage of this method of growth modelling is that the model allows for the change in scale and variance of length/height over time; each child is included in the analysis; all measurements are included, regardless of when the measurements were taken (however irregularly spaced); and the actual age at measurement is taken into account.

3. Methods, statistical methods, second paragraph: I believe it is useful to present absolute differences in terms of standard deviations, for proper internal comparisons at any age. However, it is still not possible from the paper in its current form to know whether children in Belarus are growing as expected for their age and sex, according to the reference data from the growth curves of the World Health Organization, for example. This information could make the present analysis more comparable with other studies and give readers a better the notion on the proportion of stunted children, if any. My suggestion to the authors would be replacing current SD analysis with Z scores for age and sex according to the WHO growth curves, and at least indicating some comparisons of Belarussian children with the WHO growth curves in the results section (mean height-for-age Z score, proportion of stunted children, etc). If not possible, please explain.

**Response:** (i) in Table S1, we have calculated World Health Organisation (WHO) length/height-for-age z-scores for the observed lengths/heights and described the findings in the results section; (ii) in Table 2, we now give the absolute difference in height between the highest and lowest categories of maternal education, in terms of standard deviations (SD) of the WHO growth reference, replacing the current SD analysis.

**Methods:**
The observed length/height measurements were converted to age- and sex-adjusted z-scores according to World Health Organization (WHO) Child Growth Standards 2006, using the STATA command `zanthro` \[36\].

To allow comparison of length/height differences in Belarus with an international growth standard, we report the absolute difference in terms of standard deviations of the WHO Child Growth Standards \[42\], calculated by dividing the absolute difference (cm) by the standard deviation (cm) of the WHO reference length/height measurement of the same age and sex. As length/height variance widens with age, reporting findings as standard deviations also allows a comparison of the differences on the same relative scale.

**Results:**
Additional file 1: Table S1 shows the observed lengths/heights in cm and in WHO length/height-for-age z-score, by category of maternal education. For girls aged between 6.8 and 7 years, those of the least educated mothers had a mean z-score of 0.22 (SD: 0.94), while for girls of the most educated mothers, the mean z-score was 0.61 (SD: 0.93); for boys the respective z-scores were 0.08 (SD: 0.90) and 0.64 (SD: 1.00).

Table 2 also shows the absolute differences in length/height by maternal education in terms of standard deviations of WHO length/height-for-age reference; at age 7 years, this is equivalent to 0.35SD (95% CI: 0.27, 0.43) among girls and 0.37 SD (95% CI:0.29, 0.45) among boys. The absolute SD differences
in length/height between the highest versus the lowest education categories showed some widening with age.

4. Methods, statistical methods, third paragraph: the strategy for selecting variables for the three multiple models described in this paragraph is a major concern. I agree with model 1, but I am not sure about the progressive order of inclusion of variables in models 2 and 3, considering a hierarchical framework for potential determinants of linear growth. In my opinion, mid-parental height (or maternal/paternal height separately) would temporally precede the adjustment for factors such as overcrowding, maternal smoking, and infant feeding practices. Please reformulate and/or explain your approach.

Response: We agree with your comment regarding the temporal order of the models and have reformulated models 2 and 3 to adjust for mid-parental height before the other covariables, and have made appropriate changes to the tables (Tables 3, S2 and S3), Abstract, Methods, Results and Discussion sections.

Abstract:

Results: Girls born to the most (versus least) educated mothers were 0.43 cm (95% confidence interval (CI): 0.28, 0.58) longer at birth; for boys, the corresponding difference was 0.30 cm (95% CI: 0.15, 0.46). Similarly, children of the most educated mothers grew faster from birth-3 months and 12-34 months ( p-values for trend <0.08), such that, by age 7 years, girls with the most (versus least) educated mothers were 1.92 cm (95% CI: 1.47, 2.36) taller; after controlling for urban/rural and East/West area of residence, this difference remained at 1.86 cm (95% CI: 1.42, 2.31), but after additionally controlling for mid-parental height, attenuated to 1.10 cm (95% CI: 0.69, 1.52). Among boys, these differences were 1.95 cm (95% CI: 1.53, 2.37), 1.89 cm (95% CI: 1.47, 2.31) and 1.16 cm (95% CI: 0.77, 1.55), respectively. Additionally controlling for breastfeeding, maternal smoking and older siblings did not substantively alter these findings.

Methods:

Model 2 additionally adjusted for mid-parental height, a proxy for genetic and environmental factors that influenced the parents’ own growth [14, 19-21, 43-45], while model 3 also adjusted for trial intervention arm (as an unbiased measure of prolonged and exclusive breastfeeding), maternal smoking, and number of older siblings (because previous studies have shown these factors [19-21, 46-48] to be associated with both statural growth and socioeconomic position [49, 50]).

Results:

Controlling for urban/rural and East/West area of residence attenuated the association of maternal education with growth between birth and 3 months (model 1). Additionally controlling for mid-parental height (model 2), attenuated associations of birth length and length/height velocity with maternal education for all growth periods, amongst both girls and boys. However, further controlling for prolonged and exclusive breastfeeding, maternal smoking and the number of older siblings (model 3) made little difference to the results.

5. Methods, statistical methods, third paragraph: I believe it is important to add information on adherence to PROBIT if the trial intervention arms are being considered a measure of prolonged/exclusive breastfeeding.

Response: We have added the following sentences to give details about the adherence to the breastfeeding in the two arms of the PROBIT trial:

Methods:
We included trial randomisation arm as the best assessment of the mediating effect of breastfeeding on child length/height [48]. The proportion of women who were exclusively breastfeeding was seven-fold higher in the intervention arm at 3 months compared to the control arm (43.3 vs. 6.4%) and more than 12-fold higher at 6 months (7.9 vs. 0.6%) [34].

6. Results, third and fourth paragraphs: besides results in cm, I would consider to include information in SD (or Z scores) for the absolute height differences at age 7 according to the socioeconomic variables described in the manuscript.

Response: We have given the predicted absolute difference at age 7 years in the fully-adjusted models in terms of WHO height-for-age standard deviations for each socioeconomic indicator.

Results
For the unadjusted model, the absolute difference in height at 7 years was 1.92 cm (95% CI: 1.47, 2.36) taller among girls and 1.95 cm (95% CI: 1.53, 2.37) among boys; after controlling for urban/rural and East/West area of residence (model 1), this difference remained at 1.86 cm (95% CI: 1.42, 2.31) among girls and 1.89 cm (95% CI: 1.47, 2.31) among boys. Height differences at age 7 years attenuated by 40% after controlling for mid-parental height; the difference was 1.10 cm (95% CI: 0.69, 1.52) among girls and 1.16 cm (95% CI: 0.77, 1.55) among boys (model 2). On adjustment for prolonged and exclusive breastfeeding, maternal smoking and the number of older siblings (model 3), the difference remained [1.11 cm (95% CI: 0.69, 1.53) among girls and 1.08 cm (95% CI: 0.68, 1.47) among boys]; the fully adjusted differences in terms of WHO height-for-age standard deviations among girls was attenuated to 0.20 SD (95% CI: 0.13, 0.28) and to 0.20 SD (95% CI: 0.13, 0.28) among boys.

The fully-adjusted models were used to calculate the absolute difference in height between the highest versus lowest categories of paternal education and non-manual versus manual household occupation at age 7 years; for girls, the height differences were 0.47 cm (95% CI: 0.06, 0.89) and 0.19 cm (95% CI: -0.10, 0.47), respectively; for boys, the differences were 0.15 cm (95% CI: -0.23, 0.54) and 0.42 cm (95% CI: 0.15, 0.69), respectively. The difference in terms of WHO height-for-age standard deviations among girls by paternal education was 0.09 SD (95% CI: 0.01, 0.16), and by highest household occupation was 0.03 SD (95% CI: -0.02, 0.09); the corresponding differences for boys were 0.03 SD (95% CI: -0.04, 0.10) and 0.08 SD (95% CI: 0.03, 0.13), respectively.

7. Discussion, mechanisms: could authors shed more light on why socioeconomic differences in length/height were especially detected at early infancy and early childhood, rather than the other periods analysed?

Response: We have added the following sentences to the Discussion.

Discussion:
Length/height differences widen from birth to 3 months, but on adjustment for mid-parental height, the differences were reduced substantially, suggesting that parental height explains some of the differences in growth rates during this period. Height differences also widen notably between 1-3 years; while mid-parental height explains some of the difference, other factors related to socioeconomic position, such as family diet and exposure to illness/infection, may influence offspring health and hence height growth during this period. Our findings suggest that public health interventions to improve socioeconomic conditions in early childhood, such as promoting healthy diets, educating parents about improving uptake of immunisations, preventing illness/infection and
seeking early medical care in case of illness might have a beneficial impact on later height and health.

8. Discussion, limitations: retrieving all but the last length/height measurement from child health records would be the major limitation in the present manuscript, particularly in view of the magnitude of the estimates. Would authors have any information available on reliability of these routine measurements in Belarus?

Response: Unfortunately, we have no way to assess the reliability of the routine measurements taken in Belarus. We accept the lack of information on the reliability of these measurements as a limitation of the study and have included this point in the Discussion.

Discussion:
One limitation of our study is that measurements in infancy and childhood were based on routine child health records (only measurements at the 6.5-year follow-up were standardised and audited), so associations may have been attenuated by measurement error. We are unable to assess the reliability of the routinely-collected length/height measurements in Belarus.

Minor essential revisions:
1. Methods, follow-up between 12 months to 6.5 years: please indicate the abbreviation for interquartile range, as this will be used later in the manuscript.
2. Methods, statistical methods: I suggest replacing univariable and multivariable analysis with crude and multiple analysis throughout the manuscript.
3. Results, first paragraph: please add “as shown in” or something similar as you wish before referring to Table 1.
4. Results, third paragraph: please remove “particularly”, as attenuation of estimates after controlling for urban/rural and East/West area of residence was seen only between birth and 3 months of age.
5. References: it is necessary to review the citation to comply with the Journal’s style.
6. Tables: please revise the number of decimals presented.

Discretionary revisions:
1. I suggest removing subsections from the discussion section.

Response: We have revised the manuscript to reflect all these recommendations.

Reviewer's report 2
Reviewer: Man Ki Kwok

Major Compulsory Revisions
This manuscript examines the prospective association of parental education (or occupation) with length/height trajectories from birth to 7 years using the large (n=12,463) cohort of Belarus breastfeeding promotion intervention. It is coherently written and has the potential for public health implications; however more comprehensive and explicit details on the justification of using linear spline multi-level models for generating growth trajectory, the application of addressing the identified research gap in improving population health, and the interpretation of findings within socio-historical context would be much appreciated. Moreover, the novelty and importance of the study should be convincingly presented given several previous studies from their team and others have addressed this issue.
Response: Thank you. We have taken your comments on board and have revised the manuscript to reflect your suggestions; please see the details below.

Introduction 1. Paragraph 1. The authors stated that “it is unclear at what age these socioeconomic differences emerge; if the differences change with age; and the mechanisms involved, particularly in low- and middle-income settings.” I suggest the authors should highlight the importance and relevance of the study especially in terms of public health implications here. The hypotheses or reasons behind studying starting age and mechanisms particularly in low- and middle-income settings should also be further elaborated. Do they expect universal or context-specific findings and why?

Response: We have amended the Introduction to reflect these points.

Abstract:

Conclusions: In Belarus, a middle-income former Soviet country, socioeconomic differences in offspring growth commence in the pre-natal period and generate up to approximately 2cm difference in height at age 7 years. These associations are partly explained by genetic or other factors influencing parental stature. Public health interventions aimed at improving socioeconomic conditions in early childhood might help reduce socioeconomic differences in length/height in this setting.

Background:

Adult attained height reflects fetal, infant and childhood growth and hence the influence of in utero and postpartum environment and genes [1, 2]. Height is an important marker of health, because shorter people have higher cardiovascular disease risk [3, 4] and higher overall mortality [5], albeit a lower risk of developing some cancers [4-6]. Socioeconomic differences in length and/or height (abbreviated to length/height) have been demonstrated at all ages and in various settings [7-14], with socioeconomic disadvantage associated with shorter stature.

Few studies have examined the development of socioeconomic differences in length/height from birth through infancy to childhood using repeated measures of stature; of those that have, most have been set in high-income countries [23-26], with fewer in low- or middle-income countries, such as Brazil [18, 27] or former Soviet countries, such as Russia [28]. It is important to understand not only the magnitude and timing of the emergence of socioeconomic differences in length/height (as these may clarify important growth periods when public health interventions aimed at reducing these differences, and hence inequalities in later health outcomes, might be targeted), but also the mechanisms involved (which may suggest modifiable factors suitable for intervention). By examining socioeconomic differences in childhood growth and the factors that affect growth in a middle-income former Soviet country, we aimed to understand whether the findings are specific to this context or share similarities with those in other settings.

Methods 2. Follow-up. Measurements were scheduled at 1,2,3,6,9,12 months and then 6.5 years. I wonder if the data gap between 12 months and 6.5 years would affect the generation of growth trajectory.

Response: The study paediatricians retrospectively abstracted height data from the medical records of each child, as height was routinely measured and documented at check-ups between 12 months and 6.5 years. We have now included an indication of the number of measurements recorded from birth to 7 years in Figure 1, and in the Methods section, we now include the text below. This should make it clear that many measurements were recorded between 12 months and 6.5 years from routine check-ups. We do not think this adversely affects our modelling of the growth trajectory.
Methods:
The study paediatricians also retrospectively abstracted height data from the medical records of each child, as height was routinely measured and documented at check-ups between 12 months and 6.5 years. Of 12,463 children with complete data, 10,389 children had 39,205 measurements (median, 5; IQR, 4-5; range, 1-6) abstracted from medical records between the 12-month and 6.5-year examinations.

Results:
Figure 1 shows the scatterplot of length/height measurements by child’s age; each black dot represents a single data point.

3. Statistical methods – Justification for using linear spline multilevel model is lacking. Firstly, what are the strengths and weaknesses of using current method compared with other alternative growth modeling methods or generalized estimating equation (GEE) using height gain by growth phrase? Secondly, what are the assumptions of current method? Thirdly, given growth trajectory is data-driven, and the three knots identified at 3, 12 and 34 months do not necessarily represent the biologically defined growth phrase, can the authors comment on that? Finally, as the measurement was not taken at the exact same age, instead of calculating the internally standardized coefficients in later associational analyses, why not using sex- and age-specific z-score (standard deviation score) relative to national or international growth reference? Is there any advantage for calculating the absolute difference in terms of standard deviation? Why gestational age was not adjusted for examining birth length?

Response: We have added the justification for using linear spline multilevel models, and the strengths, weaknesses and assumptions of this method in comparison to alternative methods of growth modelling to the methods section see below. We have commented further on the determination of knot points and provided references that show similar knot points have been obtained across a range of studies from different settings providing face validity that these do represent common periods of growth in children. Mixed models and generalised estimating equations (GEE) produce broadly similar findings when used with continuous outcome data, although GEE does not assume normality (1,2). We have given the absolute differences in the crude and fully-adjusted models in terms of the standard deviations of WHO international growth reference: see questions 6 above and Table 2.

Methods:
Length/height growth velocity was predicted for each child by a linear spline multilevel model with 3 knots at 3, 12 and 34 months, the knots were chosen that best fitted the data. Full details of the model selection process have been published elsewhere [37, 38]. The knot points generated four splines, estimating different length/height growth rates between 0-3 months, 3-12 months, 12-34 months and 34-84 months; designated as ‘early infancy’, ‘late infancy’, ‘early childhood’ and ‘late childhood’, respectively. The model assumes piecewise linear growth and is therefore a simplification of the underlying growth process. Although a linear spline model is an approximation of the true growth function; its coefficients are easily interpretable and have been shown to produce good model fit in this and several other cohorts [18, 23, 37-40]. Furthermore, analyses in four other cohorts in different settings have resulted in similar knot points, providing some face validity that the growth periods identified represent meaningful distinct periods of growth that are similar across children from different ethnic and socioeconomic backgrounds [18, 23, 37-40]. Individual- and occasion-level residuals were approximately normally distributed. Our approach assumes that residuals are uncorrelated and that any missing outcome data are missing at random. However, even if the autocorrelation assumption is violated, the fixed effects, which we report, are likely to be unbiased.
The advantage of this method of growth modelling is that the model allows for the change in scale and variance of length/height over time; each child is included in the analysis; all measurements are included, regardless of when the measurements were taken (however irregularly spaced); and the actual age at measurement is taken into account.

We did not adjust for gestational age, because: (i) the infants were eligible for inclusion in the trial only if they were full-term (≥37 weeks gestation), so the range of gestational ages was very narrow; and (ii) it is difficult to modify and so it would not be useful as a public health intervention.

Discussion 4. More thorough discussion on public health and/or clinical implications (e.g. growth monitoring, population-level measures in addressing socioeconomic differences or how and when to intervene) is expected in view of the 2 cm difference in height at 7 years by maternal education is of very modest magnitude.

Response: We have added to the conclusion the following discussion of the public health implications of this study:

Discussion:
Our findings suggest that public health interventions to improve socioeconomic conditions in early childhood, such as promoting healthy diets, educating parents about improving uptake of immunisations, preventing illness/infection and seeking early medical care in case of illness might have a beneficial impact on later height and health.

We are continuing to assess growth in this cohort as the children progress through puberty and into adulthood to determine the most important periods of growth associated with adult attained height and mortality. Further studies could also determine important modifiable factors, which may suggest interventions applied at suitable ages, aimed at reducing socioeconomic differences in height. Our findings may not be generalizable to other settings, for example, our height differences were fairly modest compared to those seen in the Brazilian cohort [18], mentioned above. Further investigation of longitudinal cohorts in other middle-income populations with similar or different economic histories would add to our understanding of socioeconomic differences in childhood growth.

In summary, despite low reported levels of income inequality [30], socioeconomic differences in length/height growth amongst children from Belarus were present at birth and widened through early infancy and early childhood. These differences were partly explained by mid-parental height, suggesting that factors influencing the parents’ growth during their own childhood have a bearing on these socioeconomic differences. Our findings suggest that public health interventions aimed at improving socioeconomic conditions in early childhood might help reduce socioeconomic differences in length/height in this setting.

Minor Essential Revisions
Introduction 1. Paragraph 3. Since parental education is the key indicator of socioeconomic position (SEP) used, more description on the education systems in Belarus, e.g., is there any free, universal education provision (if so, since when)? Would there be any factor affecting the opportunities of receiving education? In addition, it is interesting that Belarus has low income inequality but high adult mortality rates. Would the authors like to comment on this because it is opposite to the findings of higher mortality is associated with greater income gap in Western populations. This might have some insights for interpreting the results – how should the association
of parental education in a setting with lower income gap with child height (is height associated with mortality in Belarus or other middle-income countries) be interpreted?

Response: In response to your suggestion regarding education in Belarus, we have added the following text:

Discussion:
The parents of the PROBIT children were born under the communist system, in which education (including universities) was universal and free.

Belarus has low income inequality but high adult mortality rates, principally from cardiovascular disease. In contrast, greater income inequality is associated with higher mortality rates in Western populations, although the picture may be more complex (3). Limited evidence suggests that height is associated with mortality in middle-income countries (4-6); these studies have included China, Thailand and Taiwan. To our knowledge, no studies have examined these associations in former Soviet countries. Other studies in Belarus have shown that unemployment is associated with suicide, all cause and cardiovascular disease mortality (7,8). These associations may be mediated by factors including alcohol consumption, smoking, economic uncertainty, stress, deprivation, and reduced quality of the health care system (7,8) or may reflect reverse causality, whereby poor health leads to unemployment. The socioeconomic differences in height observed at age 7 years may translate into higher risk of cardiovascular disease later in life. We have added two references to the manuscript, which examine height differences and mortality in some middle-income countries. While we think this is a very interesting point, we have not examined these issues in the paper; it would be difficult to support any claims about inequality and mortality from our current analysis.

Methods 2. Study design. Given the inclusion criteria for infants into the original trial, it would be helpful to provide comparisons (i) between children included and the target population, and (ii) between children included and those excluded with discussion of any possibility of selection bias.

Response: We have added the following sentences:

Methods:
Inclusion criteria specified that the mothers were healthy and initiated breastfeeding, and that the infants at birth were full-term (≥37 weeks gestation) healthy singletons, weighed at least 2,500 g at birth and had a 5-minute Apgar score ≥5. Study staff estimated that only 1-2% of eligible women declined participation in the trial [33].

Results:
Table 1 compares the 16,861 children with at least two measures of length/height to those 12,463 with complete data and reveals little difference in the proportions of each covariable between the two data sets. Those with missing data were more likely among children of mothers with no more than a secondary school education compared to those of mothers educated to advanced secondary, partial university or completed university. Those with incomplete data were slightly shorter and lighter at birth and were more likely to come from urban or Eastern areas, be in the breastfeeding promotion (intervention) arm of the trial and be first born.

Discussion:
The difference between the 16,861 children with at least two measures of length/height compared to those 12,463 with complete data, showed that those with missing data were more likely to have less
educated mothers and more likely to be slightly shorter at birth. These differences should not, however, affect the associations we observed between socioeconomic status and growth trajectories.

3. Statistical methods – Could the authors explicitly state the factors (trial arms, maternal smoking, and number of older siblings) adjusted in model 2 are mediators or confounders? Using directed acyclic graph (DAG) would help clarify, and if overall effect of parental education is the interest, mediators should not be adjusted.

Response: We have considered your comment carefully and explicitly stated our conceptualisation of the covariables of trial arm, maternal smoking, and number of older siblings. In response to your suggestion, we have added the following sentences.

Methods:
Model 2 additionally adjusted for mid-parental height, a proxy for genetic and environmental factors that influenced the parents’ own growth [14, 19-21, 43-45], while model 3 also adjusted for trial intervention arm (as an unbiased measure of prolonged and exclusive breastfeeding), maternal smoking, and number of older siblings (because previous studies have shown these factors [19-21, 46-48] to be associated with both statural growth and socioeconomic position [49, 50]). These latter factors could be conceptualized as mediators, as poorer socioeconomic circumstances are associated with reduced breastfeeding [51], increased maternal smoking both pre- and postnatally [49, 50] and larger family size [19]. In addition, breastfeeding is associated with rapid linear growth in the first 3 months of life and less rapid growth to 12 months [48]. Maternal smoking, particularly during pregnancy, [20] is associated with shorter offspring stature. Overcrowding or having older siblings may also increase the frequency of childhood infection [19], lead to a sharing of resources (both material and psychosocial [47]) and affect the childhood environment and conditions, all of which may impact growth adversely.

Discussion:
We found adjustment for breastfeeding (by study trial arm), maternal smoking and older siblings did not alter the association between maternal education and offspring growth substantively. This suggests that either maternal education does not mediate its effect on offspring growth through these factors, or that by controlling for a mediator we have induced another association (e.g. induced confounding) which masks the effect of the mediator.

Results 4. Paragraph 2. Could the calculation for the following statements shown in appendix “The models were used to calculate the absolute height difference between the highest versus lowest categories of maternal education at age 7 years; for model 2, this was 1.87 cm (95% CI: 1.43 to 2.32) among girls and 1.78 cm (95% CI: 1.36 to 2.21) among boys. Height difference at age 7 years attenuated by 40% after controlling for mid-parental height in model 3 to 1.11 cm (95% CI: 0.69 to 1.53) among girls and 1.08 cm (95% CI: 0.68 to 1.47) among boys.”, it would be useful to know how to derive it from the presented Tables 2 and 3.

Response: We have added the following information to the supplementary section:

Methods:
The coefficients from the models were used to predict length/height measurements at various ages by socioeconomic position and to calculate the absolute difference between extreme categories of socioeconomic position (See supplementary information).
Supplementary information:
The models were used to calculate the absolute height difference between the highest versus lowest categories of maternal education at age 7 years using the lincom command in STATA and the following formula:

\[ \text{difference} = \text{coefficient birth length} \times 2 + 0.25 \times \text{coefficient 0-3 months} \times 2 + 0.75 \times \text{coefficient 3-12 months} \times 2 + 1.83 \times \text{coefficient 12-34 months} \times 2 + 4.167 \times \text{coefficient 34-84 months} \times 2. \]

Note:
1. The coefficients represent the interaction between maternal education and the time period.
2. Maternal education is recorded as one of three categories. In this model, the socioeconomic indicator is fitted as a continuous variable, so we assume a jump of two units from the lowest to the highest category of maternal education.

Discretionary Revisions
Methods 1. Statistical methods – since there is no sex interaction for the association between maternal education and length/height growth trajectory, I suggest presenting the overall association as the main results and the sex-stratified results as the appendix would be better, such that the results section of the abstract could provide the overall association rather than findings for boys only.

Response: Thank you for your suggestion; we agree that presenting the overall associations as the main results would make the Abstract simpler. Whilst we agree there is no sex interaction for the association between maternal education and length/height growth trajectory, girls and boys do grow at different rates. We have debated this point, and after consideration, we feel our current presentation of the findings is the most transparent and meaningful, as it allows us to examine the differences in growth trajectories of girls and boys. We have however, added more information regarding growth in girls to the Abstract.

Abstract:

Results: Girls born to the most (versus least) educated mothers were 0.43 cm (95% confidence interval (CI): 0.28, 0.58) longer at birth; for boys, the corresponding difference was 0.30 cm (95% CI: 0.15, 0.46). Similarly, children of the most educated mothers grew faster from birth-3 months and 12-34 months (p-values for trend <0.08), such that, by age 7 years, girls with the most (versus least) educated mothers were 1.92 cm (95% CI: 1.47, 2.36) taller; after controlling for urban/rural and East/West area of residence, this difference remained at 1.86 cm (95% CI: 1.42, 2.31), but after additionally controlling for mid-parental height, attenuated to 1.10 cm (95% CI: 0.69, 1.52). Among boys, these differences were 1.95 cm (95% CI: 1.53, 2.37), 1.89 cm (95% CI: 1.47, 2.31) and 1.16 cm (95% CI: 0.77, 1.55), respectively. Additionally controlling for breastfeeding, maternal smoking and older siblings did not substantively alter these findings.

In addition we should like to state: The contents of this manuscript have not been copyrighted or published previously. The contents of this manuscript are not under consideration for publication elsewhere. The contents of this manuscript will not be copyrighted, submitted, or published elsewhere while acceptance by the Journal is under consideration. There are no directly related manuscripts or abstracts, published or unpublished, by any author(s) of this paper. There are no conflicts of interests. RP as lead author confirms that the references have been checked for accuracy and completeness.

We look forward to the outcome of your consideration of our revised manuscript. We hope our responses are satisfactory but please do not hesitate to contact us if more information is required.
Yours sincerely,

Rita Patel, on behalf of the co-authors
(Please note RP will be away from 26 June-9 July 2014).


