

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

TITLE (PROVISIONAL)	The effects of birthweight and growth on childhood wheezing disorders: findings from the Born in Bradford Cohort
AUTHORS	Mebrahtu, Teumzghi; Feltbower, Richard; Parslow, Roger

VERSION 1 - REVIEW

REVIEWER	Caroline Lodge University of Melbourne Australia
REVIEW RETURNED	06-Aug-2015

GENERAL COMMENTS	<p>Mebrahtu et al. have investigated the relationship between both birth weight and weight trajectories up to the age of 2 years on the outcomes of wheezing disorders in childhood using the large Born in Bradford birth cohort (for birthweight) and a smaller subsample of this cohort (for growth trajectories). They have found that low birthweight is associated with increased risk of asthma. There is also some evidence to suggest that in this cohort, high birthweight children may be protected from wheezing disorders when compared with normal weight children. Additionally there is some evidence that children from lower mean birthweights who rapidly gain weight over the first 2 years are at increased risk of wheezing disorders.</p> <p>Overall Comments This is an interesting study with a large number of participants and solid statistical methods.</p> <p>Comments by Section Abstract Background - Line 25 – Not sure what is meant by “positive association between the two”. Does this mean as birthweight rises there is an increase in wheezing disorders (this is the opposite to what the authors have found in their recent systematic review and meta-analysis) Methods – There is no description of categories for birth weight and growth or definition of age versus visit based growth assessments as well as outcome categories. The age of outcome is not mentioned. Results – Why did you only report on two of the four “wheeze/asthma” categories. I’m not sure the visit based results add anything here. Conclusion It is not clear from the first sentence that the evidence for the increased risk of wheeze/asthma in low birth weight children is significant at a 0.05 level whereas the evidence for high birth weight is not. The second sentence which couples the initial low birth weight with a particular growth trajectory (only included in the</p>
-------------------------	---

supplement Figure S3) has not been directly addressed in the discussion.

Methods

Pg 5 Line 47 – there is no information on the outcome age for asthma/wheezing disorders. This is an important piece of information for two reasons. Firstly, to understand if the “wheezing disorders” may be more likely to be early transient wheeze or asthma; and secondly, to appreciate how this body of work fits with the existing literature in terms of both interpreting conflicting evidence and extending the relationship to older children. Indeed some of the mixed results within the literature concerning this topic could arise from differing ages of outcome measurement

Pg 5 Line 53 – The section on outcome definitions is not clear. It would be clearer if each wheeze/asthma outcome definition was expressed in a separate sentence. Additionally, on review of the diagnostic codes in supplementary table 2, the wheeze definitions have included the diagnostic codes for “inspiratory wheeze” which may be more relevant for croup rather than asthma.

Pg 6 Line 32 – It is difficult to understand the need for a visits based variable. Is this to elucidate the relationship in those who were poor attenders? Could you explain further?

Pg 6 Section starting Line 37 – Confounding variables. It is good to see the use of DAGs to obtain minimal sets of confounding variables. Have you also considered the following - In the first DAG – birth weight may also influence breastfeeding directly. Ethnicity may also directly influence both birth weight and allergic disorders. In the second DAG, breastfeeding may also directly influence both growth and wheeze outcomes. Gestational age may also be a potential confounder for the growth model as it is related to growth in early life and to allergic outcomes.

Were any of the variables included in the models checked for interaction – ie did gender/ethnicity/gest age/mat smoking/parity (also measure of siblings) modify the associations between birthweight or growth and wheeze/asthma outcomes?

Results

Line 32. It is unnecessary to write out the unadjusted ORs in their entirety as they are already expressed in the table and differ very little from the adjusted models

Table 1 – It would be easier for the reader in the outcome columns were arranged in the same order as the outcomes in Table 2 and as they are expressed in the text

Table 2 – The variables in the final models should be added as a footnote to the table

Pg 14 Line 50 - the reference to table 4 seems to be an error – should it be table 5

Discussion

Pg 17 Line 10 – Paragraph on the temporal relationship between wheezing disorders and obesity. Is it possible to untangle this relationship a little further with your data by examining for individual participants whether wheeze/asthma preceded weight gain or vice versa?

Pg17 Line 14 - By otherwise, do you mean reverse causation where wheezing disorders causes high BMI

Pg 18 Line 5. Family history of asthma is referred to in the other sections of the paper – yet maternal asthma is identified here as the important potentially confounding variable. As this is a notable

	omission to the analysis it would be good to discuss in terms of its likely effect on the results and the evidence from other studies which have controlled for this variable – is there a difference between the findings of studies which do and don't control for this variable?
--	---

REVIEWER	Raquel Granell University of Bristol, UK
REVIEW RETURNED	17-Aug-2015

GENERAL COMMENTS	<p><u>Abstract</u></p> <p>Line 31 [...] <i>statistical techniques required to approach this issue.</i></p> <p><u>Introduction</u></p> <p><u>Methods</u></p> <p>Page 5 Lines 39-41 Not clear- are there 2 sets of weight records?</p> <p>Page 5 Lines 53-57 & Page 6 Lines 3-9 It would be much clearer if definitions of outcomes were listed as follows:</p> <ol style="list-style-type: none"> 1. <i>Asthma diagnosis</i>: presence of asthma diagnosis code in the record 2. <i>Wheezing symptoms</i>: presence of wheezing diagnosis code in the record 3. Wheezing disorder based on diagnosis (<i>wheezing disorder diagnosis</i>): presence of asthma or wheezing diagnosis code in the record 4. Wheezing disorder based on treatment (<i>wheezing disorder treatment</i>): existence of at least 2 drug prescriptions indicated for the treatment of asthma between 1 week and a year apart. <p>The term 'asthma and wheezing disorders' will be used to refer to these four definitions throughout the manuscript.</p> <p>Page 6 Lines 19-20 & Lines 53-54 & Lines 57-58 Please use same names throughout the paper: asthma diagnosis, wheezing symptoms, wheezing disorder diagnosis and wheezing disorder treatment or use the term 'asthma and wheezing disorders'</p> <p>Page 7 Lines 8-16 This paragraph should be in Limitations of the study in Discussion section</p> <p>Page 7 Lines 28 Confounding (typo)</p> <p>Page 7 Lines 28-32 [...] <i>correlate variables that can be related to the missingness.</i> – Did you mean correlated variables? Which variables? Please clarify</p> <p>Page 7 Lines 48 Did you mean 'biased'?</p> <p>Page 8 Lines 5-6 Define CDC and WHO</p>
-------------------------	---

	<p>Page 8 Lines 16 Use the term ‘asthma and wheezing disorders’</p> <p>Page 8 Lines 18-25 We fitted growth mixture models (GMM) to identify the best growth patterns; in order to select the optimal number of classes we used model classification quality and fit statistics as well as interpretability [add a reference].</p> <p><u>Results</u></p> <p>General comment: The words significant, significantly, significance should not be used as these are based on an arbitrary threshold (p-value<0.05) which is nowadays obsolete. Instead use ‘little/weak/strong evidence’.</p> <p>[http://www.bmj.com/content/322/7280/226.1].</p> <p>Page 9 Lines 7 & Page 11 Line 40 what are person years of follow-up?</p> <p>Page 9 Lines 15-20 Use percentages as before. Be consistent.</p> <p>Page 9 Lines 26 Low birthweight was associated with all four disease definitions.</p> <p>Page 9 Lines 32-33 & Lines 52-54 The respective unadjusted RRs were....</p> <p><u>Table 1</u></p> <ul style="list-style-type: none"> - Title: Characteristics of 13,734 children with complete data on asthma and wheezing disorders and covariates - Please move ‘Wheezing disorder treatment’ column last for consistency <p><u>Table 2</u></p> <ul style="list-style-type: none"> - Title: Adjusted associations of covariates with asthma and wheezing disorders using 40 imputed datasets <p>Page 11 Line 47 [...] and 10% of the BiB1000 children..</p> <p>Page 11 Lines 54-58 A 3-class model was identified as the optimal model (based on statistics fit and interpretability)</p> <p>Page 12 Lines 17 [...] slow, normal and fast growth groups</p> <p>Page 12 Lines 48 The adjusted RRs for asthma diagnosis, wheezing symptoms, wheezing disorder diagnosis and wheezing disorder treatment for the ‘fast growth group’ were [...], when compared to the ‘normal growth group’.</p> <p>Page 12 Lines 55-60 The adjusted RRs for asthma diagnosis, wheezing symptoms, wheezing disorder diagnosis and wheezing disorder treatment for the ‘slow growth group’ were [...], when compared to the ‘normal growth group’.</p> <p>Page 13 Lines 15-18 A 2-class model was identified as the optimal model (based on statistics fit and interpretability)</p>
--	--

	<p>Page 13 Lines 30 inconsistent and consistent growth groups</p> <p><u>Table 4</u></p> <ul style="list-style-type: none"> - Title: Characteristics of 1,598 children from the BiB100 cohort with complete data on asthma and wheezing disorders and covariates - Please move 'Wheezing disorder treatment' column last for consistency <p>Page 14 Lines 40 The adjusted RRs for asthma diagnosis, wheezing symptoms, wheezing disorder diagnosis and wheezing disorder treatment for the 'inconsistent growth group' were [...] respectively, when compared to the 'consistent growth group'.</p> <p><u>Table 5</u></p> <ul style="list-style-type: none"> - Title: Adjusted associations of growth patterns with asthma and wheezing disorders in the BiB1000 cohort <p><u>Discussion</u></p> <p>Page 16 Lines 4-5 Use the term 'asthma and wheezing disorders'</p> <p>Page 16 Lines 14-15 [...] for low birthweight [...], compared to normal birthweight.</p> <p>Page 16 Lines 17-23 Both sets of results were non-significant, so not so inconsistent.</p> <p>Page 16 Lines 25-42 This paragraph seems redundant</p> <p>Page 16 Lines 49-57 These last two sentences are not clear, please re-write.</p> <p>Page 17 Lines 10-40 It is not clear why the authors introduce BMI at this point.</p> <p>Page 17 Lines 50-52 [...] outside Bradford would have been excluded. (typo)</p>
--	--

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
 Reviewer Name Caroline Lodge
 Institution and Country University of Melbourne
 Australia

Mebrahtu et al. have investigated the relationship between both birth weight and weight trajectories up to the age of 2 years on the outcomes of wheezing disorders in childhood using the large Born in Bradford birth cohort (for birthweight) and a smaller subsample of this cohort (for growth trajectories). They have found that low birthweight is associated with increased risk of asthma. There is also some evidence to suggest that in this cohort, high birthweight children may be protected from wheezing disorders when compared with normal weight children. Additionally there is some evidence that children from lower mean birthweights who rapidly gain weight over the first 2 years are at increased risk of wheezing disorders.

Overall Comments

This is an interesting study with a large number of participants and solid statistical methods.

Comments by Section

Abstract

Background - Line 25 – Not sure what is meant by “positive association between the two”. Does this mean as birthweight rises there is an increase in wheezing disorders (this is the opposite to what the authors have found in their recent systematic review and meta-analysis)

- The content has been cut out due to change in our formatting based on the authors' guideline, see abstract.

Methods – There is no description of categories for birth weight and growth or definition of age versus visit based growth assessments as well as outcome categories. The age of outcome is not mentioned.

- The statements have been taken out due to change in formatting based on the authors' guideline, see abstract.

Results – Why did you only report on two of the four “wheeze/asthma” categories. I’m not sure the visit based results add anything here.

- Due to lack of space in the abstract, we have only presented results for wheezing disorders diagnosis and treatment of low and high birthweight and age based growth outcome categories. The visits based results have been excluded.

Conclusion

It is not clear from the first sentence that the evidence for the increased risk of wheeze/asthma in low birth weight children is significant at a 0.05 level whereas the evidence for high birth weight is not. The second sentence which couples the initial low birth weight with a particular growth trajectory (only included in the supplement Figure S3) has not been directly addressed in the discussion.

- The first sentence has been modified to clarify that the effects of low and high birthweight are significant and insignificant, respectively.
- Supplementary figure 3 is a complementary to table 3, so discussions in relation to this table are also related to the figure.

Methods

Pg 5 Line 47 – there is no information on the outcome age for asthma/wheezing disorders. This is an important piece of information for two reasons. Firstly, to understand if the “wheezing disorders” may be more likely to be early transient wheeze or asthma; and secondly, to appreciate how this body of work fits with the existing literature in terms of both interpreting conflicting evidence and extending the relationship to older children. Indeed some of the mixed results within the literature concerning this topic could arise from differing ages of outcome measurement

- The last sentence in page 6 under “case definition and ascertainment” section has been modified to include the outcome measurement age. See pages 6

Pg 5 Line 53 – The section on outcome definitions is not clear. It would be clearer if each

wheeze/asthma outcome definition was expressed in a separate sentence.

- The outcome definitions have been numbered now. See pages 5-6

Additionally, on review of the diagnostic codes in supplementary table 2, the wheeze definitions have included the diagnostic codes for “inspiratory wheeze” which may be more relevant for croup rather than asthma.

- Diagnostic codes for “Inspiratory wheezing” would only be related to wheezing symptoms, not with asthma. According to our definitions, asthma is a subset of “wheezing disorders” so all that wheeze would not necessarily be diagnosed as asthmatic.

Pg 6 Line 32 – It is difficult to understand the need for a visits based variable. Is this to elucidate the relationship in those who were poor attenders? Could you explain further?

- The time points or time scores for the age and visits based variables have been added and additional explanation have been added. See “primary variables” sub-section page 6.

Pg 6 Section starting Line 37 – Confounding variables. It is good to see the use of DAGs to obtain minimal sets of confounding variables. Have you also considered the following - In the first DAG – birth weight may also influence breastfeeding directly. Ethnicity may also directly influence both birth weight and allergic disorders.

- We agree that birthweight can affect breast feeding (e.g. in premature or very low birthweight babies) although the effect could be temporary. When we drew a direct line (birthweight→ breast feeding) to indicate this relationship, however, the variable “breast feeding” happened to be on the causal pathway so it was excluded from the revised adjustment model.

- A direct line between ethnicity and birthweight has been drawn. However, the minimal set of variables remained the same. See supplementary figure 1 for the revised model.

In the second DAG, breastfeeding may also directly influence both growth and wheeze outcomes.

- We have created a direct link between breast feeding and growth in addition to the one between breast feeding and wheezing disorders. However, we would like to note that information breast feeding was missing so models were not adjusted. We have acknowledged this in our discussion. See supplementary figure 2 for the revised model.

Gestational age may also be a potential confounder for the growth model as it is related to growth in early life and to allergic outcomes.

- We agree that gestational age is a potential confounder. However, our analysis was restricted to the term births as we have mentioned it in the “methods section”. See page 5 paragraph 2.

Were any of the variables included in the models checked for interaction – ie did gender/ethnicity/gest age/mat smoking/parity (also measure of siblings) modify the associations between birthweight or growth and wheeze/asthma outcomes?

- Our models were checked for any interaction between exposure (birthweight or growth) and confounding variables. However, we found no indication of any interaction so models with no interaction terms were preferred for clarity.

Results

Line 32. It is unnecessary to write out the unadjusted ORs in their entirety as they are already expressed in the table and differ very little from the adjusted models

- The word “see table 2” was written by after each of the sentences. No table of unadjusted RRs results has been presented so we believe including them in the text in their entirety could be more helpful.

Table 1 – It would be easier for the reader in the outcome columns were arranged in the same order as the outcomes in Table 2 and as they are expressed in the text

- Outcome columns of Table 1 have been rearranged.

Table 2 – The variables in the final models should be added as a footnote to the table

- List of variables in the final model have been added to the table.

Pg 14 Line 50 - the reference to table 4 seems to be an error – should it be table 5

- The error has been corrected.

Discussion

Pg 17 Line 10 – Paragraph on the temporal relationship between wheezing disorders and obesity. Is it possible to untangle this relationship a little further with your data by examining for individual participants whether wheeze/asthma preceded weight gain or vice versa?

- We are only able to produce supplementary table 3 from the data we have. See page 17 lines 28-34.

Pg17 Line 14 - By otherwise, do you mean reverse causation where wheezing disorders causes high BMI Pg 18 Line 5. Family history of asthma is referred to in the other sections of the paper – yet maternal asthma is identified here as the important potentially confounding variable. As this is a notable omission to the analysis it would be good to discuss in terms of its likely effect on the results and the evidence from other studies which have controlled for this variable – is there a difference between the findings of studies which do and don't control for this variable?

- “Maternal asthma” was an error and it has been corrected as “family asthma”.
- Based on our recent meta-analysis [Ref 10], there was no significant difference between the reported adjusted risk estimates by authors that included and those not included “family Asthma” in their models. So, we speculate that omission of “family asthma” in our models may not have drastic effect. We have extended our discussion and added the reference for that. See page 18 lines 2-12

Reviewer: 2

Reviewer Name Raquel Granell

Institution and Country University of Bristol, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Please find attached document with comments to the authors

Revised by Raquel Granell 17th August 2015

Comments to the authors

Here are my comments/suggestions to help improve the manuscript

Abstract

Line 31 [...] statistical techniques required to approach this issue.

- The content has been cut out due to change in formatting based on the authors' guideline, see abstract.

Introduction

Methods

Page 5 Lines 39-41 Not clear- are there 2 sets of weight records?

- They are the same records but described in two formats, that is, in terms of age or visits. We have modified the sentence to clarify that.

Page 5 Lines 53-57 & Page 6 Lines 3-9 It would be much clearer if definitions of outcomes were listed as follows:

1. Asthma diagnosis: presence of asthma diagnosis code in the record
2. Wheezing symptoms: presence of wheezing diagnosis code in the record
3. Wheezing disorder based on diagnosis (wheezing disorder diagnosis): presence of asthma or wheezing diagnosis code in the record
4. Wheezing disorder based on treatment (wheezing disorder treatment): existence of at least 2 drug prescriptions indicated for the treatment of asthma between 1 week and a year apart.

- The definitions of the outcomes have been numbered now.

The term 'asthma and wheezing disorders' will be used to refer to these four definitions throughout the manuscript.

- We believe the term wheezing disorders could be inclusive enough for asthma and the other three outcome definitions.

Page 6 Lines 19-20 & Lines 53-54 & Lines 57-58 Please use same names throughout the paper: asthma diagnosis, wheezing symptoms, wheezing disorder diagnosis and wheezing disorder treatment or use the term 'asthma and wheezing disorders'

- We have amended and used the same names now.

Page 7 Lines 8-16 This paragraph should be in Limitations of the study in Discussion section

- We have already included it in the discussion section. However, we also believe that mentioning it here would add clarity of our modelling process.

Page 7 Lines 28 Confounding (typo)

- Typo has been corrected.

Page 7 Lines 28-32 [...] correlate variables that can be related to the missingness. – Did you mean correlated variables? Which variables? Please clarify

•We are referring to the two variables, that is, maternal hypertension and diabetes. The word “correlate” can be unnecessary here so we have excluded it now.

Page 7 Lines 48 Did you mean ‘biased’?

•No, we mean “unbiased”.

Page 8 Lines 5-6 Define CDC and WHO

•Definitions have added.

Page 8 Lines 16 Use the term ‘asthma and wheezing disorders’

•We believe wheezing disorders is inclusive enough for the four diseases definitions.

Page 8 Lines 18-25 We fitted growth mixture models (GMM) to identify the best growth patterns; in order to select the optimal number of classes we used model classification quality and fit statistics as well as interpretability [add a reference].

•For the GMM and identifying the optimal number of classes, we have included references 37 and 38.
Results

General comment: The words significant, significantly, significance should not be used as these are based on an arbitrary threshold (p-value<0.05) which is nowadays obsolete. Instead use ‘little/weak/strong evidence’. [<http://www.bmj.com/content/322/7280/226.1>].

•The terms have been replaced by ‘little/weak/strong evidence’ throughout the manuscript.

Page 9 Lines 7 & Page 11 Line 40 what are person years of follow-up?

•These are the cumulative number of follow-up years in the cohort.

Page 9 Lines 15-20 Use percentages as before. Be consistent.

•Numbers have been converted into percentages now.

Page 9 Lines 26 Low birthweight was associated with all four disease definitions.

•It has been amended now.

Page 9 Lines 32-33 & Lines 52-54 The respective unadjusted RRs were....

•It has been amended now.

Table 1

- Title: Characteristics of 13,734 children with complete data on asthma and wheezing disorders and covariates

•The title has been amended.

- Please move ‘Wheezing disorder treatment’ column last for consistency

- The sequence of the columns has been amended.

Table 2

- Title: Adjusted associations of covariates with asthma and wheezing disorders using 40 imputed datasets

- The title has been amended.

Page 11 Line 47 [...] and 10% of the BiB1000 children..

- “of” has been added to the sentence.

Page 11 Lines 54-58 A 3-class model was identified as the optimal model (based on statistics fit and interpretability)

- We think that if collapse the two sentences into one, the optimal numeration of classes results table will be lost.

Page 12 Lines 17 [...] slow, normal and fast growth groups

- Normal, fast and slow growth groups would correctly describe for class 1, class 2 and class 3 respectively.

Page 12 Lines 48 The adjusted RRs for asthma diagnosis, wheezing symptoms, wheezing disorder diagnosis and wheezing disorder treatment for the ‘fast growth group’ were [...], when compared to the ‘normal growth group’.

- Sentence amendment has been made although we would like to note that class 2 is fast growth group.

Page 12 Lines 55-60 The adjusted RRs for asthma diagnosis, wheezing symptoms, wheezing disorder diagnosis and wheezing disorder treatment for the ‘slow growth group’ were [...], when compared to the ‘normal growth group’.

- Sentence amendment has been made although we would like to note that class 3 is slow growth group.

Page 13 Lines 15-18 A 2-class model was identified as the optimal model (based on statistics fit and interpretability)

- We think that if collapse the two sentences into one, the optimal numeration of classes results table will be lost.

Page 13 Lines 30 inconsistent and consistent growth groups

- The sentence has been amended.

Table 4

- Title: Characteristics of 1,598 children from the BiB100 cohort with complete data on asthma and wheezing disorders and covariates

- The title has been amended.

- Please move ‘Wheezing disorder treatment’ column last for consistency

- The columns have been rearranged.

Page 14 Lines 40 The adjusted RRs for asthma diagnosis, wheezing symptoms, wheezing disorder diagnosis and wheezing disorder treatment for the 'inconsistent growth group' were [...] respectively, when compared to the 'consistent growth group'.

•The sentence has been amended.

Table 5

- Title: Adjusted associations of growth patterns with asthma and wheezing disorders in the BiB1000 cohort

•We have slightly modified the title.

Discussion

Page 16 Lines 4-5 Use the term 'asthma and wheezing disorders'

•We believe the term wheezing disorders is inclusive enough for asthma and the other three outcome definitions.

Page 16 Lines 14-15 [...] for low birthweight [...], compared to normal birthweight.

•The sentence has been modified.

Page 16 Lines 17-23 Both sets of results were non-significant, so not so inconsistent.

•We are referring to the direction of the risk estimates.

Page 16 Lines 25-42 This paragraph seems redundant

•We believe it is necessary as it discusses the results of growth patterns before making comparison with previous studies findings.

Page 16 Lines 49-57 These last two sentences are not clear, please re-write.

•The sentences have been modified now.

Page 17 Lines 10-40 It is not clear why the authors introduce BMI at this point.

•The "BMI" in line 14 refers to the findings from our previous meta-analysis work although we would like to note that weight becomes equivalent to BMI once the values are converted into standardised scores and percentiles.

Page 17 Lines 50-52 [...] outside Bradford would have been excluded. (typo)

•Typo has been amended.

VERSION 2 – REVIEW

REVIEWER	Caroline Lodge University of Melbourne, Australia
REVIEW RETURNED	20-Oct-2015

GENERAL COMMENTS	Thank you for asking me to review this interesting paper on the Bradford cohort. A number of changes have been made which have greatly improved the paper. I have some remaining concerns detailed below. Abstract:
-------------------------	--

	<p>Although you mention results on slow versus fast growth in the results (page2 line3), the methods for defining this are not mentioned in the abstract methods. (although the methods are interesting and worth mentioning up front)This is true also for the last sentence in the conclusion which covers ground not present in methods or results of abstract.</p> <p>Introduction: (Page3, lines41-46). In presenting the previous findings from your systematic review it would be pertinent to note also that the heterogeneity referred to was only present for the studies concerning the low birth weight estimates. The high birth weight estimate did not have significant heterogeneity (which makes your current finding different to the literature)</p> <p>Methods: I appreciate that the authors have undertaken to clarify the wheezing groups by setting them out more formally. Unfortunately, I think there may be an error in the current classification. Should category 2 read: "presence of wheezing diagnosis codes in the record" instead of what is currently in the manuscript? This error makes it difficult to interpret the findings It would be interesting to know also the prevalence of NICU treatment and respiratory issues at birth in the babies by birth weight category</p> <p>Page 8 , Line 9 – "variable" should be "variables"</p> <p>Discussion: Fast versus Slow versus Normal growers I am aware that you do not have information on type on infant feeding, however it would be very interesting to discuss how feeding may have affected these growth groups. For example Class 2 may have been a group of infants who were initially breastfed but due to concerns over failure to thrive, they were changed to formula feeding with the consequent massive increase in growth. Furthermore, the slow growth group may have been the completely breastfed group. In this sense it may be feeding mode which explains wheeze/asthma risk rather than the weight change – weight may be a marker or a mediator. It would be interesting to further discuss the possible role of breastfeeding, especially considering that it was identified as a variable to be considered in the model but you were unable to do so. Page 19 line 11- This is the beginning of a very long sentence which will need restructuring : "Likewise.....".. I would suggest finishing this sentence after "model results", and also placing "unadjusted" before "adjusted" so that the confounders included in the sentence are associated with "adjusted". If you want to keep the following words, they will need to be rewritten. The effect of lack of adjustment for potentially confounding variables in a model will depend on whether these variables are true confounders in the model not on the number of them missing, so the statement about not adjusting for two confounders is not correct as it stands- is this sentence necessary-could it be reworded. Also the word "into" is not correctly used in the sentence</p>
--	---

VERSION 2 – AUTHOR RESPONSE

Abstract:

Although you mention results on slow versus fast growth in the results (page2 line3), the methods for defining this are not mentioned in the abstract methods. (although the methods are interesting and worth mentioning up front)This is true also for the last sentence in the conclusion which covers ground

not present in methods or results of abstract.

- Methods for defining and classifying of growth patterns have been added to the abstract.

Introduction:

(Page3, lines41-46). In presenting the previous findings from your systematic review it would be pertinent to note also that the heterogeneity referred to was only present for the studies concerning the low birth weight estimates. The high birth weight estimate did not have significant heterogeneity (which makes your current finding different to the literature)

- The statement has been modified. It now reads as “However, we acknowledged there was substantial heterogeneity among the low birthweight risk estimates which was not accounted for by study characteristics.”

Methods:

I appreciate that the authors have undertaken to clarify the wheezing groups by setting them out more formally. Unfortunately, I think there may be an error in the current classification. Should category 2 read: “presence of wheezing diagnosis codes in the record” instead of what is currently in the manuscript? This error makes it difficult to interpret the findings
It would be interesting to know also the prevalence of NICU treatment and respiratory issues at birth in the babies by birth weight category

- Thank you. The error has been corrected. The statement now reads as “presence of wheezing diagnosis codes in the record”.

Page 8 , Line 9 – “variable” should be “variables”

- It has been corrected as “variables”.

Discussion:

Fast versus Slow versus Normal growers

I am aware that you do not have information on type on infant feeding, however it would be very interesting to discuss how feeding may have affected these growth groups. For example Class 2 may have been a group of infants who were initially breastfed but due to concerns over failure to thrive, they were changed to formula feeding with the consequent massive increase in growth. Furthermore, the slow growth group may have been the completely breastfed group. In this sense it may be feeding mode which explains wheeze/asthma risk rather than the weight change – weight may be a marker or a mediator. It would be interesting to further discuss the possible role of breastfeeding, especially considering that it was identified as a variable to be considered in the model but you were unable to do so.

- The World Health Organization promotes breast milk as the best source of nutrition for babies, infants and children[1]. Studies also show that breast milk is protective against obesity[2], respiratory tract infection and asthma[3]. In addition, it has been reported that bottle fed children are more likely to be obese due to lack of self-regulation on the amount of intake[4]. Thus, infants who switched from breast milk to bottle feeding are more likely to show fast growth. Based on these, it can be suggested that class 2 (fast growth group) were bottle fed group of children. However, the suggestion that class 2 were a group of children who initially failed to thrive due to being breast fed, and that class 3 (slow growth group) were exclusively breast fed may not be correct.

- Breast feeding, as a confounding variables, can have effect on child's growth and asthma (or wheezing disorders) status. Our DAG model is reflecting that by including direct lines from breast feeding towards the exposure (childhood growth) and outcome (wheezing disorders) variables. Although the aim of adjusting for confounders is to reduce bias in the risk estimate, the effect could be also be minimal. Thus, while acknowledging that our risk estimates could be biased (page 19, lines 5-6), we also have highlighted the fact that there was no difference between adjusted and unadjusted risk estimates in some studies (page 19, lines 7-15). The statements have been slightly modified now.

Page 19 line 11- This is the beginning of a very long sentence which will need restructuring :
"Likewise.....". I would suggest finishing this sentence after "model results", and also placing "unadjusted" before "adjusted" so that the confounders included in the sentence are associated with "adjusted". If you want to keep the following words, they will need to be rewritten. The effect of lack of adjustment for potentially confounding variables in a model will depend on whether these variables are true confounders in the model not on the number of them missing, so the statement about not adjusting for two confounders is not correct as it stands- is this sentence necessary-could it be reworded. Also the word "into" is not correctly used in the sentence

- The words after "model results" have been removed. The "unadjusted" has been placed before "adjusted"

References:

- 1.WHO. World Health Organization (WHO): 10 facts on breastfeeding. 2015 [cited 2015 23 October]; Available from: <http://www.who.int/features/factfiles/breastfeeding/en/>.
- 2.Arenz, S., et al., Breast-feeding and childhood obesity[mdash]a systematic review. *Int J Obes Relat Metab Disord*, 2004. 28(10): p. 1247-1256.
- 3.Ip, S., et al., Breastfeeding and maternal and infant health outcomes in developed countries. *Evidence report/technology assessment*, 2007(153): p. 1.
- 4.Salone, L.R., W.F. Vann Jr, and D.L. Dee, Breastfeeding: An overview of oral and general health benefits. *The Journal of the American Dental Association*, 2013. 144(2): p. 143-151.