

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The association of the 'Additional Height Index' with atopic diseases, non-atopic asthma, ischemic heart disease and mortality
<b>AUTHORS</b>	Fenger, Runa; Vidal, Carmen; Gonzalez-Quintela, Arturo; Husemoen, Lise-Lotte; Skaaby, Tea; Aadahl, Mette; linneberg, allan

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Katharine Pike University of Southampton, UK
<b>REVIEW RETURNED</b>	24-Sep-2013

<b>GENERAL COMMENTS</b>	<p>The introduction is in the main concisely written. There could be greater clarity regarding the timescale of the increased prevalence of atopic disease and how this relates to the birthdates of the study population. The description of 'overly healthy' is perhaps overly speculative when what is being described is that factors associated with increased growth in childhood might also be associated with allergy. References to increased childhood growth would help anchor the hypothesis; reference 7 for example relates to an interpretative conclusion of another study (that increased nutrition causing increased childhood growth is associated with reduced risk of certain disease states) rather than data describing change in childhood growth during this time.</p> <p>Pre and postnatal growth should be distinguished; this is of significance because each could have differing effects upon disease risk.</p> <p>The twofold objectives are more logically ordered 1) to establish whether additional height may serve as a proxy for childhood health by testing for expected inverse associations in conditions such as IHD and 2) to look for inverse associations with allergy given that both childhood height (and health) and allergy are stated to be increasing. As stated above the strength of the hypothesis would be greater if these increases in childhood height/health and allergy were referenced. (I do appreciate that the concept of childhood health is hard to measure hence the need for the additional height proxy but temporal changes in height or diet should be available?)</p> <p>MATERIALS AND METHODS</p>
-------------------------	--

	<p>The population is well described and of a good size with reasonable retention. The limitations of reported parental height and questionnaire data on disease outcomes are clearly stated. There is no mention of ethical review or consent procedures.</p> <p>Did the authors consider whether the equation used to calculate expected height was appropriate for this population or whether an internal reference could have been constructed from parental heights of study participants? Is it possible that the additional height measure as calculated measures difference from an historical ideal, rather than individual differences in height associated with individual factors independent of common contemporary conditions. Unfortunately I was not able to access the cited reference describing calculation of expected height, equally I am limited in my linguistic skills to English language publications! My understanding, however, is that this is based upon work by Tanner and that there is no basis stated for the addition or subtraction of a particular amount be that 6.5, 7 or 7.5 cm depending upon publication. In its current state the manuscript does not robustly defend the use of the unvalidated additional height index against use of total height adjusted for parental height. For example expected height based upon mid parental height has been criticised upon the grounds of not accounting for regression to the mean. It is not clear (save from slightly tighter confidence intervals) that additional height represents a marked improvement over total height in terms of better representing mechanistic factors associated with childhood health.</p> <p><b>RESULTS</b> Clearly described. Adequate statistical analysis including sensitivity analyses.</p> <p><b>DISCUSSION</b> Limitations are appropriately discussed. Results are placed in the context of previous work associating additional calories with cancer and altered microbiome with allergy; the two conditions are not contrasted however. It would be interesting to see a discussion of whether different mechanisms are likely to underlie the associations with allergy and cancer mortality. Do they follow the same timescale for example?</p> <p>As mentioned with reference to the introduction it would be helpful to see pre and postnatal growth considered separately.</p> <p><b>ILLUSTRATIONS AND TABLES</b> Tables easy to understand and appropriately captioned.</p>
--	--

	<p><b>REFERENCES</b></p> <p>Generally appropriate referencing.</p> <p>Introduction could be sharpened though with data to underpin the assertions made about temporal changes in growth and allergy.</p> <p>Minor points</p> <p>Page 3 second bullet point should read indicator of rather than or childhood conditions?</p> <p>References inconsistent formatting eg ref 23 contains full names of authors whilst others only initials</p> <p>Citations in the text should be placed after punctuation marks</p>
--	---

<b>REVIEWER</b>	Catarina Almqvist Malmros Karolinska Institutet, Stockholm Sweden
<b>REVIEW RETURNED</b>	27-Oct-2013

<b>GENERAL COMMENTS</b>	<p>The aim of this study was 1) to define a height measure indicating an individual's height below or above that which could be expected based on parental height; adult height index (AHI) and 2) to investigate possible associations of AHI with atopic vs. non-atopic health outcomes as well as with ischemic heart disease (IHD) and IHD-mortality.</p> <p>This study proposes that the AHI, calculated as the difference between an individual's attained height and what is expected based on the height of their parents, can be used in epidemiological studies and would possibly reflect living circumstances in childhood. This is an interesting prospect and the method could be used in other epidemiological studies where information on growth in childhood is not available. The manuscript however needs some clarifications.</p> <p><b>Introduction</b></p> <p>The hypothesis of the study does not seem clearly linked to the previous research which is presented in the introduction. Is it to be assumed that the authors believe that catch-up growth during infancy in small babies is related to positive "extra height" in adult life in these individuals? If there is previous literature supporting this theory it should be referenced, If not the authors' reasons for believing this to be the case should be stated.</p> <p><b>Materials and methods</b></p> <p>1. Were the MONICA10 (1993-1994) study participants selected from the previous participants of MONICA1 (1982-1984), or were they recruited in an independent wave of data collection using the</p>
-------------------------	---

	<p>same criteria? If they were also part of MONICA1, the percentage of the original study population from which data is available for the current study should be shown in addition to the participation rates from each step. In order to make this completely clear, a flow chart may be helpful.</p> <p>2. The attained height index is calculated by subtracting an individual's expected height from their measured height. The calculation for expected height is provided, and in this context a reference is given to national Danish growth charts. Were these charts the source material based on which the expected height formula was constructed? Has the formula to calculate expected height been validated in any other population or is it a reflection of the distribution of height versus parental height in young Danes in 1982? Discuss this and the implications for your calculated measure.</p> <p>3. Is the variable for leisure time physical activity included in the regression models? It does not appear to be referenced in the figures but is mentioned in the methods section.</p> <p>4. How was the variable for mid, low and high values of additional height categorized?</p> <p>5. Systolic blood pressure and blood lipid levels are included in the models according to the figures, but not mentioned in the methods section. Where did these data come from and how were they categorized?</p> <p>6. How was additional height index modeled in the logistic and cox regressions? The figures mention "one standard deviation" but this is not brought up in the methods section. In case this is the categorization used, why has this been chosen instead of additional height in centimeters?</p> <p>Results</p> <p>1. Descriptive statistics related to Figure 1, Table 1 and 2 in first page of results is confusing and need to be clarified. It is not clear how the reference category was constructed in Figures 2 and 3.</p> <p>2. The mean attained height index shows variability over age strata. What could be the reasons for this variability? Please discuss this and how it is related to the point in time during which the reference data set for expected height was collected.</p> <p>3. Most of the associations shown in the regression models are not in fact statistically significant, but this is not obvious from the presentation in the results section and abstract. More emphasis could be put on this aspect of the results.</p> <p>Discussion</p> <p>1. Discuss possible selection bias the study.</p> <p>2. The authors discuss that the AHI has not been validated as a measure of childhood living conditions. Has it been validated as a proxy for infant catch-up growth or any other growth pattern abnormality in particular?</p> <p>3. Are different periods in life likely to have different strengths of effects on the AHI? In the discussion, relative starvation and skipping meals is brought up as important aspects of childhood living conditions, but are these particularly prevalent in infancy, for example?</p>
--	--

	<p>4. Height on its own appeared to have similar effects as the attained height index, but the confidence intervals for these associations were wider. Are there any advantages of using height alone?</p> <p>5. Birth weight and catch-up growth are mentioned in the introduction but completely left out from discussion. Please mention and discuss in light of the AHI.</p> <p>Minor comments:</p> <ol style="list-style-type: none"> <li>1. There are some spelling errors (in the abstract and article focus section, for example “Copentagen” instead of Copenhagen) and unclear use of language (in particular in the first paragraphs of the introduction).</li> <li>2. Key messages are fairly strongly stated and do not seem to align with statistical findings after adjustment.</li> <li>3. The name of the test kit used to detect IgE antibodies should be mentioned in the Methods section even though a reference to an original publication is given.</li> <li>4. The abbreviation “SPT reactivity” turns up in the discussion without prior explanation.</li> </ol>
--	--

### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name Katharine Pike

Institution and Country University of Southampton, UK

Please state any competing interests or state ‘None declared’: None declared

#### INTRODUCTION

The introduction is in the main concisely written. There could be greater clarity regarding the timescale of the increased prevalence of atopic disease and how this relates to the birthdates of the study population. The description of ‘overly healthy’ is perhaps overly speculative when what is being described is that factors associated with increased growth in childhood might also be associated with allergy. References to increased childhood growth would help anchor the hypothesis; reference 7 for example relates to an interpretative conclusion of another study (that increased nutrition causing increased childhood growth is associated with reduced risk of certain disease states) rather than data describing change in childhood growth during this time.

**RESPONSE:** We agree that this is a very relevant point. We have added references of increased growth in childhood. We have added description of temporal changes in affluence and allergy to the introduction. Further, we have specified our hypothesis that affluence lead to changes in health focused behaviour / changes in dietary patterns and subsequently to allergy. We have also specified that this ‘health hypothesis’ may be tested as an association of increased growth with allergy.

Pre and postnatal growth should be distinguished; this is of significance because each could have differing effects upon disease risk.

**RESPONSE:** We have distinguished pre and postnatal growth and specified that the Additional Height Index is meant to measure growth from the postnatal period to adulthood.

The twofold objectives are more logically ordered 1) to establish whether additional height may serve as a proxy for childhood health by testing for expected inverse associations in conditions such as IHD and 2) to look for inverse associations with allergy given that both childhood height (and health) and allergy are stated to be increasing. As stated above the strength of the hypothesis would be greater if these increases in childhood height/health and allergy were referenced. (I do appreciate that the

concept of childhood health is hard to measure hence the need for the additional height proxy but temporal changes in height or diet should be available?)

RESPONSE: We have added referenced description of temporal changes in affluence and allergy to the introduction. Further, we have specified our hypothesis that affluence lead to changes in health focused behaviour / changes in dietary patterns and subsequently to higher susceptibility to allergy. We have also specified that this 'health hypothesis' may be tested as an association of increased growth with allergy. We have emphasised this in the discussion as compared to the first version of the paper.

#### MATERIALS AND METHODS

The population is well described and of a good size with reasonable retention. The limitations of reported parental height and questionnaire data on disease outcomes are clearly stated. There is no mention of ethical review or consent procedures.

RESPONSE: We thank the reviewer for making this point and have added the information to the methods section.

Did the authors consider whether the equation used to calculate expected height was appropriate for this population or whether an internal reference could have been constructed from parental heights of study participants? Is it possible that the additional height measure as calculated measures difference from an historical ideal, rather than individual differences in height associated with individual factors independent of common contemporary conditions. Unfortunately I was not able to access the cited reference describing calculation of expected height, equally I am limited in my linguistic skills to English language publications! My understanding, however, is that this is based upon word by Tanner and that there is no basis stated for the addition or subtraction of a particular amount be that 6.5, 7 or 7.5 cm depending upon publication. In its current state the manuscript does not robustly defend the use of the unvalidated additional height index against use of total height adjusted for parental height. For example expected height based upon mid parental height has been criticised upon the grounds of not accounting for regression to the mean. It is not clear (save from slightly tighter confidence intervals) that additional height represents a marked improvement over total height in terms of better representing mechanistic factors associated with childhood health.

RESPONSE: We agree that defining the Additional Height Index depend on the method of estimating the 'expected height'. Further, we agree that there is no basis for addition/subtraction of a very particular amount such as 6.5 cm. Thus, before writing the paper we tested three ways of achieving the 'expected height'. We found that all three ways of estimating the 'expected height' and subsequently the Additional Height Index yielded fairly similar estimates of the associations of the Additional Height Index with the health outcomes presented in the paper. Further, we tried to estimate the possible regression to the mean in heights in our study population and correct all three 'Additional Height Indexes' for possible regression to the mean. The subsequent analyses also gave fairly similar associations of the Additional Height Index with the health outcomes presented in the paper. Thus, we found that the Additional Height Index is robust. With the revision of the manuscript we add a supplementary file with ways of calculating the Additional Height Index and with an example of a way to try to correct for a possible regression to the mean in heights.

Further, we speculate that the 'Additional Height Index' may capture some information that height alone does not. For instance, consider a relatively tall individual, who is, however, shorter than expected if the genetic inheritance (heights of the parents) is taken into account. In this case, height alone would assign positive value to this individual but the Additional Height Index would assign a negative value to this individual. The opposite situation would occur with a relatively short individual, who is, however, taller than what could be expected from that individual's genetic inheritance. We also speculate that the Additional Height Index may have an advantage over a measure as leg length.

Leg length is believed to measure growth in infancy and the prepubertal period whereas the Additional Height Index may measure imbalanced growth throughout the postnatal period to adulthood. With the revision of the manuscript we have included a discussion of the Index in the discussion section.

## RESULTS

Clearly described. Adequate statistical analysis including sensitivity analyses.

## DISCUSSION

Limitations are appropriately discussed. Results are placed in the context of previous work associating additional calories with cancer and altered microbiome with allergy; the two conditions are not contrasted however. It would be interesting to see a discussion of whether different mechanisms are likely to underlie the associations with allergy and cancer mortality. Do they follow the same timescale for example?

RESPONSE: In the revised manuscript we discuss the timescale and included references of cancer development in a cohort of Danish citizens with information of growth, and where some of the participants are born in the same time area as those in our study.

As mentioned with reference to the introduction it would be helpful to see pre and postnatal growth considered separately.

RESPONSE: In the revised manuscript we consider pre and postnatal growth separately in both the introduction and discussion.

## ILLUSTRATIONS AND TABLES

Tables easy to understand and appropriately captioned.

## REFERENCES

Generally appropriate referencing.

Introduction could be sharpened though with data to underpin the assertions made about temporal changes in growth and allergy.

RESPONSE: We have added this to the introduction

## Minor points

Page 3 second bullet point should read indicator of rather than or childhood conditions?

References inconsistent formatting eg ref 23 contains full names of authors whilst others only initials

Citations in the text should be placed after punctuation marks

RESPONSE: We thank the reviewer for making us aware of these points.

Reviewer: 2

Reviewer Name Catarina Almqvist Malmros

Institution and Country Karolinska Institutet, Stockholm Sweden

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

The aim of this study was 1) to define a height measure indicating an individual's height below or above that which could be expected based on parental height; adult height index (AHI) and 2) to investigate possible associations of AHI with atopic vs. non-atopic health outcomes as well as with ischemic heart disease (IHD) and IHD-mortality.

This study proposes that the AHI, calculated as the difference between an individual's attained height and what is expected based on the height of their parents, can be used in epidemiological studies and would possibly reflect living circumstances in childhood. This is an interesting prospect and the method could be used in other epidemiological studies where information on growth in childhood is not available. The manuscript however needs some clarifications.

## Introduction

The hypothesis of the study does not seem clearly linked to the previous research which is presented in the introduction. Is it to be assumed that the authors believe that catch-up growth during infancy in small babies is related to positive "extra height" in adult life in these individuals? If there is previous literature supporting this theory it should be referenced, If not the authors' reasons for believing this to be the case should be stated.

### RESPONSE:

We have tried to clarify that we use the examples of catch-up growth and of growth slower than normal in the prepubertal period as examples of imbalanced growth by adding the words: "different patterns of" to a sentence in the third paragraph of the introduction. We do not believe that catch-up growth during infancy in small babies is related to positive "extra height". We only think that extra height all in all as assessed by the Additional Height Index could be a measure of imbalanced growth of any type.

## Materials and methods

1. Were the MONICA10 (1993-1994) study participants selected from the previous participants of MONICA1 (1982-1984), or were they recruited in an independent wave of data collection using the same criteria? If they were also part of MONICA1, the percentage of the original study population from which data is available for the current study should be shown in addition to the participation rates from each step. In order to make this completely clear, a flow chart may be helpful.

RESPONSE: We have changed the description of the sampling of the study population and have inserted a reference to a study that has a flow chart of the population from MONICA1 through MONICA10.

2. The attained height index is calculated by subtracting an individual's expected height from their measured height. The calculation for expected height is provided, and in this context a reference is given to national Danish growth charts. Were these charts the source material based on which the expected height formula was constructed? Has the formula to calculate expected height been validated in any other population or is it a reflection of the distribution of height versus parental height in young Danes in 1982? Discuss this and the implications for your calculated measure.

RESPONSE: The growth charts described in 1982 were the background and inspiration for our construction of the "Additional Height Index". The growth charts depict an expected height. We add the idea that growth above or below that expected height may be associated with certain health outcomes. However, we agree with the reviewer that the expected height itself could not necessarily be based solely on the growth charts made in 1982 since e.g. changes in height over time may not be accounted for. Thus, we calculated the expected height with several methods including one to account for different age strata in our population (or other populations). With the revision of the manuscript we add a supplementary file showing these calculation methods.

3. Is the variable for leisure time physical activity included in the regression models? It does not appear to be referenced in the figures but is mentioned in the methods section.

RESPONSE: Yes, the variable for leisure time physical activity is included in the regression models. We thank the reviewer for mentioning this point; we have now made sure to write it in the figure

legends.

4. How was the variable for mid, low and high values of additional height categorized?

RESPONSE: The variable for mid, low and high values of the Additional Height Index was made by categorisation of the Additional Height Index in tertiles. We have changed the formulation in the second paragraph of the statistics section to emphasise this.

5. Systolic blood pressure and blood lipid levels are included in the models according to the figures, but not mentioned in the methods section. Where did these data come from and how were they categorized?

RESPONSE: The data came from MONICA10 and were used for adjustment of the Cox regressions modelling IHD event or IHD mortality. There was no categorisation used. We thank the reviewer for mentioning this point; we have now made sure to write it more specifically in the methods section.

6. How was additional height index modeled in the logistic and cox regressions? The figures mention "one standard deviation" but this is not brought up in the methods section. In case this is the categorization used, why has this been chosen instead of additional height in centimeters?

RESPONSE: We have included some lines in the statistics paragraph of the methods section (kindly also refer to our answer to the next question) and believe that it is now clear that we have chosen to report our results of the regression analyses per "one standard deviation" of the Additional Height Index. We agree with the reviewer that it would also have been possible to report the results as Odds/Hazard Ratio for e.g. every one or five or ten centimetres (or e.g. inches). However, we think that reporting results by standard deviations give a better measure of the impact of the variable so that the readers of BMJOpen more easily can judge the practical significance of the variable as, for instance, also used in: Pike KC, Crozier SR, Lucas JSA et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. *Thorax*. 2010 Dec;65(12):1099-106. doi: 10.1136/thx.2010.134742.

## Results

1. Descriptive statistics related to Figure 1, Table 1 and 2 in first page of results is confusing and need to be clarified. It is not clear how the reference category was constructed in Figures 2 and 3.

RESPONSE: We have changed our description of results, especially the second paragraph of the results, and find that the statistics leading to the results as well as the results all in all are easier to read.

2. The mean attained height index shows variability over age strata. What could be the reasons for this variability? Please discuss this and how it is related to the point in time during which the reference data set for expected height was collected.

RESPONSE: We agree with the reviewer that the Attained Height Index varies for study participants born in 1922, 1932, 1942 and 1952. We think that these changes over time could be explained by increases in overall living standards in Denmark between 1922 and e.g. 1970 at which time all study participants may have been become adults. However, as part of our sensitivity analyses we checked that the associations of the Additional Height Index and the health outcomes did not essentially change between study participants born in the four different age strata. In a supplementary file we show three ways to calculate the Additional Height Index, among those a method to especially account for different age strata. As the different calculation methods result in essentially similar associations between the Additional Height Index and the health outcomes, we find that the Additional Height Index is independent of the point in time during which an original dataset to describe growth in Danish children was collected.

3. Most of the associations shown in the regression models are not in fact statistically significant, but

this is not obvious from the presentation in the results section and abstract. More emphasis could be put on this aspect of the results.

RESPONSE: We agree that only the associations of the Additional Height Index with non-atopic asthma and wheeze were statistically significant. Although the HR for IHD/IHD mortality 0.89 (0.78-1.01) was very close to significance (Figure 2). However, we have tried to put more emphasis on this matter both in the key-points and in the results section. In the abstract, we were able to squeeze the word “possible” into the conclusion section.

## Discussion

1. Discuss possible selection bias the study.

RESPONSE: We agree that selection bias is a possibility. We have added a discussion of this to the limitations section of the discussion

2. The authors discuss that the AHI has not been validated as a measure of childhood living conditions. Has it been validated as a proxy for infant catch-up growth or any other growth pattern abnormality in particular?

RESPONSE: The Additional Height index has not been validated in other studies for other growth patterns since we constructed the Index for the purpose of this study and for possible future use. However, other height measures, such as total height, leg length or leg-trunk ratio, are well known to be inversely associated with cardiovascular outcomes. Since increasing levels the Additional Height Index also point toward a lower risk of IHD and IHD-mortality, we propose this as indirect validation of the Additional Height Index.

3. Are different periods in life likely to have different strengths of effects on the AHI? In the discussion, relative starvation and skipping meals is brought up as important aspects of childhood living conditions, but are these particularly prevalent in infancy, for example?’

RESPONSE: We speculate that the Additional Height Index may measure imbalanced growth any time from infancy to adulthood since it may measure any deviance from the height the child would attain under normal circumstances. Yet, it seems likely that changes of e.g. nutritional intake would have the greatest impact on growth and, thus, on the Additional Height Index if these changes occur in periods of faster growth as infancy and the prepubertal period. In the discussion we would like to bring up that we notice a change of dietary patterns towards frequent meals and we speculate that this may change the microbiom in a way that gives higher susceptibility of allergy. This more likely seem to be relevant for older children (in Denmark and countries like Denmark).

4. Height on its own appeared to have similar effects as the attained height index, but the confidence intervals for these associations were wider. Are there any advantages of using height alone?

RESPONSE: We acknowledge that height may seem as a reasonable proxy for the Additional Height Index, especially since a part of tall individuals are tall due exactly to “additional height”. We have changed our discussion of this topic and try to emphasise that relatively short individuals may – despite their shortness – have a ‘high amount of positive additional height’, and relatively tall individuals may still be shorter than that, which could be expected by genetic inheritance (parents’ height). In both cases, height alone may not capture the information hidden in “the Additional Height Index”. For instance, for relatively short individuals, who are taller than expected, the Additional Height Index would assign a positive value. However, height per se would assign a relatively low value (cm/inches) compared to values assigned to other participants in a specific study. Thus, even though the difference between the Additional Height Index and height is not very remarkable in our current study, we still think that the Additional Height Index may be preferable as a measure of health/growth. Furthermore, we do find much broader confidence intervals and less certain results with height alone.

5. Birth weight and catch-up growth are mentioned In the introduction but completely left out from

discussion. Please mention and discuss in light of the AHI.

RESPONSE: We thank the reviewer for making this point and have tried, first of all, to change the emphasis in the introduction from catch-up growth only to also include different kinds of unbalanced growth (as also mentioned in the answer of another question). Further, in the revised manuscript we have mentioned decreased stunting in the discussion section.

Minor comments:

1. There are some spelling errors (in the abstract and article focus section, for example “Copentagen” instead of Copenhagen) and unclear use of language (in particular in the first paragraphs of the introduction).
2. Key messages are fairly strongly stated and do not seem to align with statistical findings after adjustment.
3. The name of the test kit used to detect IgE antibodies should be mentioned in the Methods section even though a reference to an original publication is given.
4. The abbreviation “SPT reactivity” turns up in the discussion without prior explanation

RESPONSE: We thank the reviewer for making these points and have corrected the spelling errors, mentioned the ADVIA Centaur® Allergy Screen Assay in the methods section, changed the “SPT reactivity” formulation to “skin prick test reactivity” and softened the Key messages relating to atopic sensitisation, atopic dermatitis and rhinoconjunctivitis.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Katharine Pike University of Southampton, United Kingdom
<b>REVIEW RETURNED</b>	16-Dec-2013

<b>GENERAL COMMENTS</b>	<p><b>Introduction/Abstract</b> This paper has been strengthened by inclusion of references in support of temporal change in diet, growth and allergies. The references are not of direct relevance to the population described (i.e. Northern European) but I suspect few are available. The hypothesis is more prominent and coherently stated. In particular the explanation of why a tall individual who is nevertheless shorter than expected based upon parental heights is likely to have been exposed to different environmental, possibly dietary factors, during childhood and adolescence and thus if these factors are relevant to the development of allergic and other disease states may be at greater risk of these diseases than an individual of identical height but taller parents. I would disagree that few studies have considered growth and allergy, allow concede that asthma has been the principle focus of most studies. As such, the suggestion that factors affecting growth might also be affect allergy risk is not novel and should not be overstated in the abstract. It is still unclear in the abstract why increased AHI is likely to be associated with allergic diseases (although this is clear in the introduction).</p> <p><b>Methods</b> Transparency much improved by further information on calculation of AHI, additional details on physical examination and blood tests and statistical methods. I believe tertiles to refer to the dividing values and that it would be more accurate to state divided into equal thirds but do not feel strongly about this point.</p> <p><b>Results</b> Addition of sentence describing change in risk per SD of AHI helpful.</p> <p><b>Discussion</b> The main value of this paper is in providing a new epidemiological measure which acknowledges the importance of early life factors for</p>
-------------------------	---

	<p>later disease rather than to provide new mechanistic insights. On this point it is perhaps worth mentioning that the statement in the discussion presenting dietary health behaviours as an alternative to theories based upon hygiene may overstate the role of diet as surely frequent childhood infections would also affect growth? The section discussing wheeze considers adiposity prominently when what was measured was additional height. It may be relevant to consider the relationship between airway calibre and height which underlies adjustment of lung function for height. As such much of the relationship between AHI and wheeze outcomes (the most significant) may reflect growth of airways rather than immune change; this would be consistent with the less significant results seen for allergic outcomes such as allergic dermatitis/rhinitis.</p> <p>Minor points          There is a spelling error in the first sentence of the article focus section          There remains inconsistency in reference format ref 33 does not include author initials and appears to contain author first names</p>
--	--

### VERSION 2 – AUTHOR RESPONSE

Reviewer Name Katharine Pike

Institution and Country University of Southampton, United Kingdom

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

#### Introduction/Abstract

This paper has been strengthened by inclusion of references in support of temporal change in diet, growth and allergies. The references are not of direct relevance to the population described (i.e. Northern European) but I suspect few are available. The hypothesis is more prominent and coherently stated. In particular the explanation of why a tall individual who is nevertheless shorter than expected based upon parental heights is likely to have been exposed to different environmental, possibly dietary factors, during childhood and adolescence and thus if these factors are relevant to the development of allergic and other disease states may be at greater risk of these diseases than an individual of identical height but taller parents. I would disagree that few studies have considered growth and allergy, allow concede that asthma has been the principle focus of most studies.

RESPONSE: We agree that many studies have considered prenatal and early childhood growth, particularly 'birth weight', in relation the asthma risk. Initially, we wanted to describe that few studies have considered later growth in relation to the risk of developing asthma in otherwise healthy children. However, we have deleted this sentence as it may be confusing to the reader.

As such, the suggestion that factors affecting growth might also be affect allergy risk is not novel and should not be overstated in the abstract.

RESPONSE: In the 'background' paragraph of the abstract we have included an extra sentence about intrauterine growth and the risk of asthma and allergy that is already well described in the literature.

It is still unclear in the abstract why increased AHI is likely to be associated with allergic diseases (although this is clear in the introduction).

RESPONSE: We have included an extra sentence in the key points about AHI and the possible association with allergic diseases based on changes in dietary patterns as it seemed very difficult to include more information in the abstract.

## Methods

Transparency much improved by further information on calculation of AHI, additional details on physical examination and blood tests and statistical methods. I believe tertiles to refer to the dividing values and that it would be more accurate to state divided into equal thirds but do not feel strongly about this point.

RESPONSE: We agree with the reviewer and have changed this in the revised version of the paper.

## Results

Addition of sentence describing change in risk per SD of AHI helpful.

RESPONSE: We have added a few sentences to the Results Section giving an example of how to interpret a change of 1 SD of AHI.

## Discussion

The main value of this paper is in providing a new epidemiological measure which acknowledges the importance of early life factors for later disease rather than to provide new mechanistic insights. On this point it is perhaps worth mentioning that the statement in the discussion presenting dietary health behaviours as an alternative to theories based upon hygiene may overstate the role of diet as surely frequent childhood infections would also affect growth?

RESPONSE: We agree with the reviewer that surely childhood infections affect growth, among other known and unknown factors. Thus, we have changed the sentence of the discussion from 'alternative' to 'supplementary' theory and added a sentence about the possibility that AHI actually measures the result of childhood infections.

The section discussing wheeze considers adiposity prominently when what was measured was additional height. It may be relevant to consider the relationship between airway calibre and height which underlies adjustment of lung function for height. As such much of the relationship between AHI and wheeze outcomes (the most significant) may reflect growth of airways rather than immune change; this would be consistent with the less significant results seen for allergic outcomes such as allergic dermatitis/rhinitis.

RESPONSE: We agree with the reviewer that a likely reason for increased susceptibility to asthma/wheeze is reduced airway calibre that is present with overall reduced growth. Therefore, we have now included this in the discussion along with the lines of less optimal childhood conditions leading to both reduced growth (decreased AHI) and late-onset disease. In our opinion, this changes focus from adiposity to height.

## Minor points

There is a spelling error in the first sentence of the article focus section

There remains inconsistency in reference format ref 33 does not include author initials and appears to contain author first names

RESPONSE: We thank the reviewer for making these points, we have corrected the mistakes