Author’s response to reviews

Title: BMI, waist circumference at 8 and 12 years of age and FVC and FEV1 at 12 years of age; the PIAMA birth cohort study

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Author’s response to reviews: see over
Response to the reviewers

First, we would like to thank the reviewers for the time and effort to review our manuscript. Below, we have provided our response to each of the comments given by the reviewer.

Reviewer 1:
Minor Essential Revisions:
1. Abstract (Methods): The authors should add a sentence to the methods section in the abstract describing the statistical models which were used to analyse the associations between BMI and WC with lung function parameters.

Author’s response: According to the reviewer’s suggestion we have added the following sentence to the methods section: ‘the associations between BMI and WC and FVC, FEV\(_1\) and FEV\(_1\)/FVC ratio were studied using local and linear regression analyses, separately for girls and boys’. (Page 2, line 37-39)

2. Abstract (Methods/Results): It is not clear whether the regression models were adjusted for confounding variables (e.g. age and height) and if so, whether the presented results refer to the adjusted models.

Author’s response: To the methods section has been added: ‘The regression models were adjusted for age, height and pubertal development and maternal educational level. (Page 2, line 39-40)

3. Abstract (Results): The results presented in the abstract are limited to FVC. Maybe one sentence could be added mentioning the results for the association between BMI/WC with FEV\(_1\) and FEV\(_1\)/FVC (as boys and girls with a high BMI and WC have a significantly lower FEV\(_1\)/FVC ratio compared to those with a normal BMI and WC).

Author’s response: Following the reviewer’s suggestion we have added these sentences to the results section: ‘No statistically significant associations were observed between (persistently) high BMI or large WC and FEV\(_1\). The FEV\(_1\)/FVC ratio was statistically significantly lower in children with a high BMI or large WC than in children with a normal BMI or WC. Girls and boys with a persistently high BMI or large WC status had statistically significantly lower FEV\(_1\)/FVC ratios’. (Page 2, line 46-50)

4. Methods: Please state how pubertal development was defined. Was it defined based on information requested via the PDS?

Author’s response: Pubertal development was assessed using the pubertal development scale (PDS). This has been added to the section on covariates in the methods section and a reference where the scale is described has been added. (Page 6, line 139)

5. Results: There is a strong focus on the results for the associations of BMI and WC with FEV\(_1\) and FVC. As FEV\(_1\)/FVC is a measure of airway obstruction, results of this or previous studies on this parameter might also be discussed in the abstract, introduction and discussion.

Author’s response: A sentence on the FEV\(_1\)/FVC ratio has been added to the abstract (see our response to comment 3.). in the revised version of the manuscript we paid more attention to the results on the FEV\(_1\)/FVC ratio in the discussion. (Page 10, line 261-269)

6. Table 1: The definition of overweight and obesity is mentioned in the figure legend, but a separate symbol is needed for this footnote (as it is stated with the definition of “frequent asthma symptoms”) and should also be added in the table behind the terms “overweight” and “obesity”.

Author’s response: In the revised version of table 1 overweight and obesity have a separate symbol for their definition. (Page 17)
7. Table 1: Please add a footnote for the variables “BMI category 8 and 12 years” and “Waist circumference category 8 and 12 years” to explain how the categories were defined.  
Author’s response: A footnote has been added explaining the BMI and WC categories in Table 1. (Page 18, line 438)

8. Table 1: The study characteristics for categorical variables could be stated as n/N (%) instead of n (%) to get some information about the number of missing values. For instance, the total number of subjects on which the comparison of BMI and WC categories at 8 and 12 years is based (variables “BMI category 8 and 12 years” and “Waist circumference category 8 and 12 years”) differs from the numbers referring just to the 12 year follow-up (n=655 girls and n=633 boys) as children with a BMI or WC below the 10th percentile were excluded and information on BMI and WC at 8 as well as at 12 years of age was not available for all 1288 subjects.  
Author’s response: According to the reviewer’s suggestion ‘N’ has been added to table 1 for the categorical variables. (Page 17-18)

9. Methods (Statistical analyses): The authors could add a sentence which tests were used to compare the study characteristics of males and females presented in Table 1.  
Author’s response: The differences in prevalence of baseline characteristics between boys and girls were assessed by a t-test, this information has been added to the methods on page 6. (Line 165)

Reviewer 2:
Major Compulsory Revisions
1. The figures are one of the major strengths of the study. However, here BMI and/or WC is referred to as z-score (until then, only sd is mentioned). Adjusted FVC and FEV1 is stated to be in liters, but is on average 1. The FEV1/FVC ratio is also 1. Does this represent a standardized factor rather than measured volume or ratio?  
Author’s response: In the revised version of the manuscript we have included changes in the figures as suggested by the reviewer. The term z-scores has been replaced by sd-scores, in line with the terminology used in the text of the paper. The FVC and FEV1 on the y-axis are the partial predictions. We thank the reviewer for pointing out the error in the Y axis label.

2. The methods section states that standard deviation scores were at 12 yrs calculated according to the Dutch Fourth nationwide Growth study. However, it remains difficult to understand if the SD for BMI and WC later described was defined; a) as SD according to these reference values or b) according to the distribution of the calculated SDs in the present population. It is of particular importance that this is clear as the method appears to be different from the one used in the 8 yr follow up of the same cohort.  
Author’s response: Both at 8 and 12 years standard deviation scores for BMI and WC were calculated based on the external reference values obtained from the Dutch nationwide Growth study. Subsequently, the 10% children in our study population with the lowest sd-scores for BMI and WC were defined as having a low BMI and WC and the 10% children in our study population with the
highest sd-scores for BMI and WC were defined as having a high BMI and WC. This is now more clearly explained in the methods. (Page 5, line 119)

3. Under table 2 it is stated that for example, 10th percentile of WC is -0.89 SD, while for BMI it is -1.33 SD. Does this mean that the reference equations fitted better for one variable for the other? Does this have any implications for the results?
Author’s response: The distribution of BMI and WC in our study population does indeed not entirely match the distribution of BMI and WC in the Dutch reference population. In particular, the 10% girls with the lowest WC in our study population are less thin than the lowest 10% in the reference population, whereas the boys with a BMI above the 90th percentile in our study population have higher BMI’s than the boys with a BMI above the 90th percentile in the reference population. These differences may have had some effect on the strength of the associations we observed (as compared to the associations that would be observed in the reference population). However, in our analyses we compared children at the extremes of the BMI and WC distribution with children in the ‘normal’ range and we did not have the intention to define absolute cut-off points for high and low BMI and WC.

4. The findings that high BMI/WC was related to a low FEV1/FVC ratio is not discussed. Also, that low BMI/WC was associated with the largest negative effects on FVC and FEV1 is missing from the discussion section.
Author’s response: See response to the first reviewer question 5. In the first section of the discussion the results on the FEV1/FVC ratio are discussed in the revised version of the manuscript. (Page 10, line 261-269)
Low BMI and small WC were not the aims of our study as described in the introduction and therefore not discussed in the discussion section. However, to be complete, we analysed and presented the results of low BMI and small WC.

5. Atopy was defined as IgE concentration. This is not in line with the definition of atopy according to the EAACI nomenclature “SGO Johansson et al, Allergy 2001: 56: 813–824”. If atopy is to be used instead of sensitization, please add rationale for this.
Author’s response: In the text we used the term atopy to simplify reading. In the revised version of the manuscript we replaced atopy by sensitization.

6. Serum specific IgE levels more than 0.7 IU/mL is used as a definition of atopy. The methodology is not specified. For ImmunoCAP FEIA, the normal value is less than 0.1 kU/L, according to the manufacturer's instructions (www.phadia.com). What was the rationale for this specific cutoff?
Author’s response: Specific IgE levels for house dust mite, cat, grass (Dactylis glomerata) and birch pollen were measured in blood samples by a radioallergosorbent test-like method used at the Sanquin Laboratories (Amsterdam, The Netherlands). There is no prescribed international standard for the definition of sensitization, but a specific IgE level >0.35 IU/ml is frequently used as a cut-off to define sensitization. In our study, sensitization to inhalant allergens was defined as a specific IgE concentration of at least 0.70 IU/ml on at least 1 of the inhalant allergens.
The limit was set at 0.70 IU/ml, because an IgE concentration of at least 0.70 IU/ml is indicative of allergic symptoms.(Kerkhof M et al. Clin Exp Allergy 2000;30: 1387-94). This cut-off value of 0.70 IU/ml was also used in our previous study in the 8-year-old children and in a number of other studies conducted in the PIAMA population (e.g. Bekkers MB et al. Eur Respir J. 2012;39: 1468-74 and Scholtens S e al. J Allergy Clin Immunol. 2009;123: 1312-8).

Minor Essential Revisions
Background:
7. The aim(s) of the study is very long. It could be shortened and more focused.
Author’s response: For clarity, we chose to introduce the two aims of our study separately, therefore the aim of the study may seem long. However, we removed the last sentence of the introduction as we feel, with the reviewer, that one sentence on the second aim is enough. (Page 3)

Methods:
8. The methods section lack definitions of covariates and could benefit from a more structured outline. For example, the spirometry method is mentioned in three different places. It is also unclear to what extent ERS/ATS criteria was used or not (if not, please comment in the discussion section).
Author’s response: The definitions of the covariates were described in the paragraph ‘height, weight, waist circumference and lung function’ in the methods section. In the revised version we have added a header ‘covariates’ to have more structure.

We removed the information on the spirometry measurement from the paragraph ‘study design and population’.

We used the ATS/ERS criteria but we also included children who did not meet these criteria but did have a difference <200mL between the two largest FEV1 measurements. To study the consequences of this decision we performed sensitivity analyses with the children with FEV1 measures within 150mL difference. (page 9, line 246)

9. The study design and population is clearly described but the original intention of the cohort is not described.
Author’s response: The initial objectives of the study were to evaluate the effectiveness of allergen reduction measures for the prevention of asthma and mite allergy in children of allergic mothers, and to investigate the natural history of childhood asthma and risk factors for the development of asthma. Later, the study aims were expanded to include early markers of cardiovascular disorders. (Page 4, line 94)

10. How was pubertal status defined?
Author’s response: Pubertal development was assessed by child report using the pubertal development scale (PDS). In the methods section we added the reference for this rating scale (Page 6, line 139). In the section on confounders (Page 6, line 158) and in the discussion (Page 11, line 299) we replaced pubertal status by pubertal development as we did not exactly define pubertal status but used a rating scale for pubertal development.

11. “Statistical model: Ln (lung function testing variable) = constant + ln (height) + ln (age) + BMI<10th percentile + BMI>90th percentile + ‘error’. The result is the percent difference in FVC, FEV1 or FEV1/FVC ratio in children in the lowest and highest 10% of BMI compared with FVC, FEV1 or FEV1/FVC ratio in children with ‘normal’ BMI.”
– Is the result of the model the percent difference or is it converted to and expressed as the percent difference?
Author’s response: The percent change in lung function was calculated from the estimated coefficients beta as follows: % change=[exp(beta)-1]*100.

12. Sensitivity analysis is mentioned but not further explained. What does this refer to?
Author’s response: As mentioned in the methods section sensitivity analyses were performed for children with a difference <150mL between two FEV1 measurements, as this is the strict ATS/ERS criteria. As described in the results section (page 9) the estimates of BMI and WC on FVC and FEV1 did not differ between the two groups (FEV1 difference <150mL and FEV1 difference ≥150mL).

Discretionary Revisions
13. Methods section: Consider revising the statement that the FEV1/FVC ratio is used to indicate restriction.
Author’s response: According to the reviewer’s suggestion we have revised this sentence. It now reads “As outcome measures we used FVC as a measure of lung volume, FEV$_1$ as a measure of airway patency and the FEV$_1$/FVC ratio to indicate possible obstruction of the airways.” (Page 5, line 124)

14. Table 1. Back height is not previously mentioned. Is this the same as sitting height?
Author’s response: back height is indeed the same as sitting height. In Table 1 back height has been replaced by sitting height for consistency. (Page 17)