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PEAK FLOW VARIABILITY IN CHILDHOOD AND BODY MASS INDEX IN ADULT LIFE

Enrico Lombardi MD^a, Debra A. Stern MS^b, Duane Sherrill PhD^b, Wayne J. Morgan MD^b,
Anne L. Wright PhD^b, Judith Garcia-Aymerich MD^{c,d}, Ignasi Serra Pons MS^c,
Stefano Guerra MD PhD^{b,c}, and Fernando D. Martinez MD^b

^a Pediatric Pulmonary Unit, “Anna Meyer” Pediatric University-Hospital, Florence, Italy

^b Asthma and Airway Disease Research Center, The University of Arizona, Tucson, Arizona

^c ISGlobal Centre for Research in Environmental Epidemiology (CREAL),

and Universitat Pompeu Fabra, Barcelona, Spain

Correspondence and requests for reprints: Fernando D. Martinez, MD, Asthma and Airway Disease
Research Center, University of Arizona Health Sciences, 1501 North Campbell Avenue, Room 2349, P.O.
Box 245030, Tucson, AZ 85724–5030. Tel. +1.520.626-6387; Fax +1.520.626-6623; email
fdmartin@email.arizona.edu

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Key words: *Peak flow variability, body mass index, asthma, children*

SHORT SUMMARY

Peak flow variability in childhood is a significant and independent predictor of subsequent body mass index increase up to age 26. Shared developmental and genetic factors may explain, at least in part, the association between these two phenotypes.

To the Editor:

Several cross-sectional studies have shown an association between obesity and asthma and meta-analyses of prospective studies have concluded that obesity precedes the development of asthma and wheezing in both adults and children¹. However, a recent study of 2 longitudinal cohorts suggested that children with asthma are at increased risk of subsequent development of obesity². The nature and the direction of the association between the two conditions thus remain unclear³. Diurnal peak flow variability (PFvar) is considered an important measurement of airway lability in the screening and diagnosis of asthma in population-based studies. We have previously found increased PFvar and response to albuterol in girls who became overweight or obese during the school years as compared with those who did not⁴, suggesting a link between an abnormal regulation of the airway tone and weight gain in the school years. The aim of the current study was to determine whether airway lability in children is associated with subsequent body mass index (BMI) increase up to young adult life in the longitudinal Tucson Children's Respiratory Study birth cohort⁵.

Detailed methods and definitions are reported in the Online Repository. Questionnaires on participants' respiratory symptoms and physical activity were completed by their parents at age 11 [Yr11: mean (SD) 10.7 (0.5) yr] and 16 [Yr16: 16.6 (0.6) yr] and by participants themselves at age 22 [Yr22: 22.1 (0.9) yr] and 26 [Yr26: 26.5 (0.9) yr]. At each survey skin prick tests were performed and BMI (kg/m^2) was calculated. At a mean age of 10.8 yr peak expiratory flow data were collected for 1 week and PFvar was calculated as previously reported⁶ (see the Online Repository). BMI and PFvar values were logarithmically transformed (base 10) to obtain a normal distribution. The potential confounding effects of parental education, ethnicity, metabolic equivalents of task (METs), and smoke exposure were also tested. This study was approved by the Human Subjects Committee at the University of

Arizona, and informed consent was obtained from the parents before age 18 and, subsequently, from the participants themselves.

Among the 600 children with PFvar information at Yr11, the number of subjects with subsequent BMI information was 500 at Yr16, 485 at Yr22, and 453 at Yr26 (see the Online Repository). The characteristics of the study subjects at Yr11 in comparison with those who were excluded because of missing information on BMI or PFvar (Table E1) and at each subsequent survey (Table E2) are reported in the Online Repository. At Yr11 the geometric mean (95%CI) PFvar was 7.6 (7.3, 8.0) %, range 0.7-41.9%, and 62 children (10.3%) had a high PFvar. In univariate analyses, a significant linear correlation was found between log-transformed PFvar at Yr11 and log-transformed BMI at Yr11 ($r=0.10$, $p=0.015$), Yr16 ($r=0.14$, $p=0.001$), Yr22 ($r=0.14$, $p=0.002$), and Yr26 ($r=0.11$, $p=0.019$). Figure E1 (Online Repository) shows that, as compared with participants with normal PFvar, those with high PFvar at Yr11 were more likely to be obese at Yr16 [RR (95% CI) from generalized estimating equations (GEE) models: 2.00 (1.17, 3.39)], Yr22 [2.31 (1.53, 3.48)], and Yr26 [1.77 (1.23, 2.56)], but not at Yr11 [1.38 (0.75, 2.54)]. Similarly, no significant association was found between high PFvar at Yr11 and obesity earlier in childhood (see the Online Repository).

In random effects multivariate models with log-transformed BMI as the continuous dependent variable, we found subjects with high PFvar to have only marginally increased BMI at Yr11 but significantly higher BMI at all other ages than subjects with normal PFvar, with the largest differences achieved by age 26 (Figure E2). The best fitting model (Table E3) included both age and age squared terms, consistent with deceleration of BMI increase from childhood to young adult life; also (Table E3), the effect of high PFvar on subsequent BMI was mainly explained by the interaction between high PFvar and age, indicating that after adjustment for covariates high PFvar at Yr11 was associated with a steeper increase over time (or, in other words, a higher velocity of growth)

of BMI. After further adjustment of the model for BMI at Yr11 and/or smoke exposure, results remained virtually unchanged (data not shown). However, when random effects models were stratified by sex we found notable differences in the association between PFvar and BMI increase between females and males (Table 1 and Figure 1). The interaction between high PFvar and age was highly significant in females ($p < 0.001$) but not in males ($p = 0.968$), showing that the effect of high PFvar on the subsequent BMI increase was only present in the former group (Table 1). These effects were confirmed when repeating the analysis in subjects who were neither overweight/obese nor asthmatic at age 11 (see the Online Repository).

In summary, we found high PFvar at age 11 to predict a steeper subsequent BMI increase up to young adult life independent of multiple covariates, including current asthma at age 11. Interestingly, the effects of high PFvar at Yr11 were much stronger on subsequent than concomitant levels of BMI suggesting that our findings are very unlikely to be explained by concomitant effects of obesity on airway lability. In other words, if the relationship between PFvar and BMI were simply explained by the fact that subjects with a higher BMI are de-conditioned and have a lower lung function, one might expect a better correlation between high PFvar and elevated BMI during childhood surveys, which was not the case in our study. These findings support the possibility that the association between asthma and obesity may be bidirectional or due to shared factors that preexist both conditions³ (see the Online Repository for previous literature and the limitations of the study). Obesity and asthma are known to share common genetic mechanisms^{7,8}; furthermore, developmental and early life factors have also been suggested as affecting the development of both obesity and asthma^{8,9}. We propose that such common factors might cause both an alteration in the regulation of airway tone and a greater tendency to gain weight during the growing years and that the asthma-related phenotype might thus precede the obesity phenotype.

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114 Enrico Lombardi MD^a,115 Debra A. Stern MS^b116 Duane Sherrill PhD^b117 Wayne J. Morgan MD^b118 Anne L. Wright PhD^b119 Judith Garcia-Aymerich MD^{c,d}120 Ignasi Serra Pons MS^c121 Stefano Guerra MD PhD^{b,c}122 Fernando D. Martinez MD^b

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124 ^a Pediatric Pulmonary Unit, “Anna Meyer” Pediatric University-Hospital, Florence, Italy125 ^b Asthma and Airway Disease Research Center, The University of Arizona, Tucson, Arizona126 ^c ISGlobal Centre for Research in Environmental Epidemiology (CREAL), and Universitat Pompeu
127 Fabra, Barcelona, Spain

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FIGURE LEGEND

Fig. 1 - Linear prediction of base 10 log-transformed body mass index (BMI) vs age for subjects with high (red circles) and normal (blue circles) PFvar at age 11 after stratifying by sex (A: females; B: males). Linear predictions were calculated from random effects models adjusted for maternal and paternal education, and ethnicity as fixed effects and current asthma, atopy, and Metabolic Equivalents of Task (METs) at each survey as time-dependent covariates. P-values related to group differences at each time point were tested using linear contrast.

Table 1 - Longitudinal analysis by random effects models of base 10 log-transformed BMI at ages 11, 16, 22, and 26 as the dependent variable and potential confounders at the four surveys stratified by sex (females n=307, males n=277). Age was centered at the youngest age, 9.2 years, to facilitate interpretation of the main effect coefficient of PFvar.

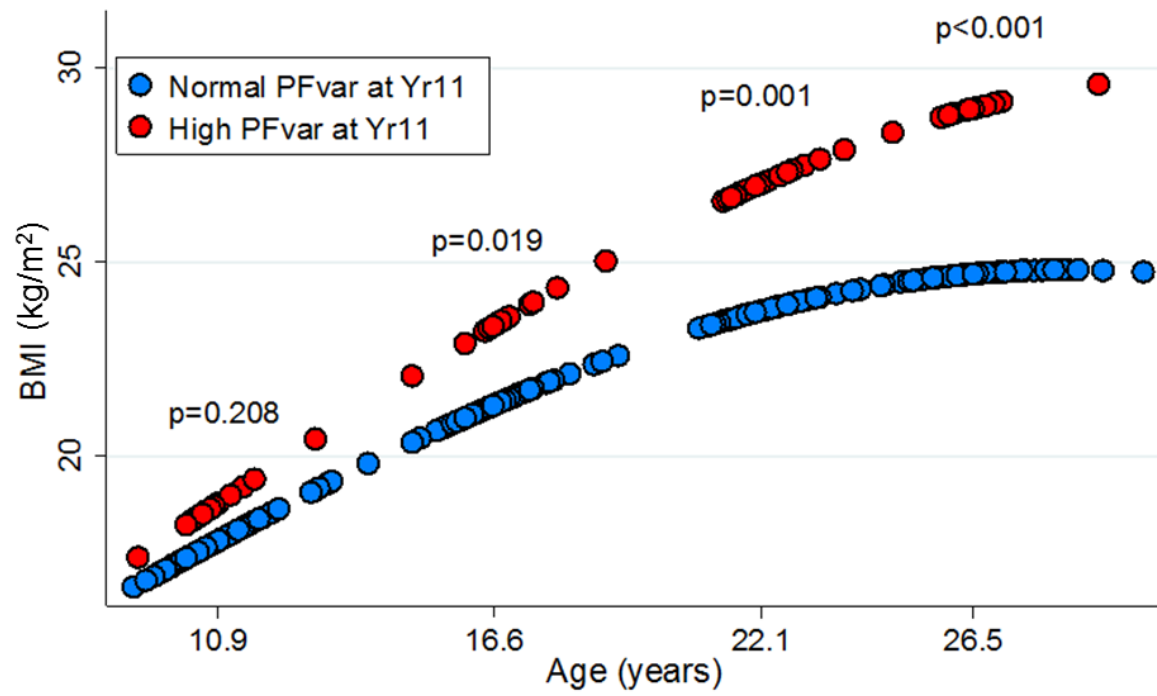
	<i>Females (n=308, obs=898)</i>			<i>Males (n=276, obs=772)</i>		
	<i>Coefficient</i>	<i>95% CI</i>	<i>p</i>	<i>Coefficient</i>	<i>95% CI</i>	<i>p</i>
High PFvar at Yr11	0.018	-0.019, 0.054	0.338	0.018	-0.014, 0.050	0.275
Age	0.018	0.016, 0.020	< 0.001	0.020	0.017, 0.022	<0.001
Age²	-0.0005	-0.0006, -0.0004	< 0.001	-0.0005	-0.0006, -0.0004	<0.001
High PFvar x Age	0.003	0.001, 0.005	< 0.001	0.0004	-0.002, 0.002	0.968
Concurrent Asthma	0.020	0.007, 0.033	0.002	-0.002	-0.011, 0.014	0.802
Concurrent Atopy	-0.006	-0.016, 0.005	0.312	-0.003	-0.015, 0.009	0.649
Concurrent METs[*]	-0.002	-0.006, 0.003	0.503	-0.004	-0.008, 0.0009	0.114
Maternal Education ≤12yrs	0.020	-0.004, 0.047	0.095	-0.0008	-0.024, 0.022	0.948
Paternal Education ≤12yrs	0.015	-0.012, 0.042	0.276	0.034	0.011, 0.057	0.004
At least 1 Hispanic Parent[§]	0.013	-0.012, 0.037	0.306	0.018	-0.003, 0.040	0.097
Other Ethnicity[§]	0.033	0.003, 0.064	0.032	-0.013	-0.043, 0.017	0.398

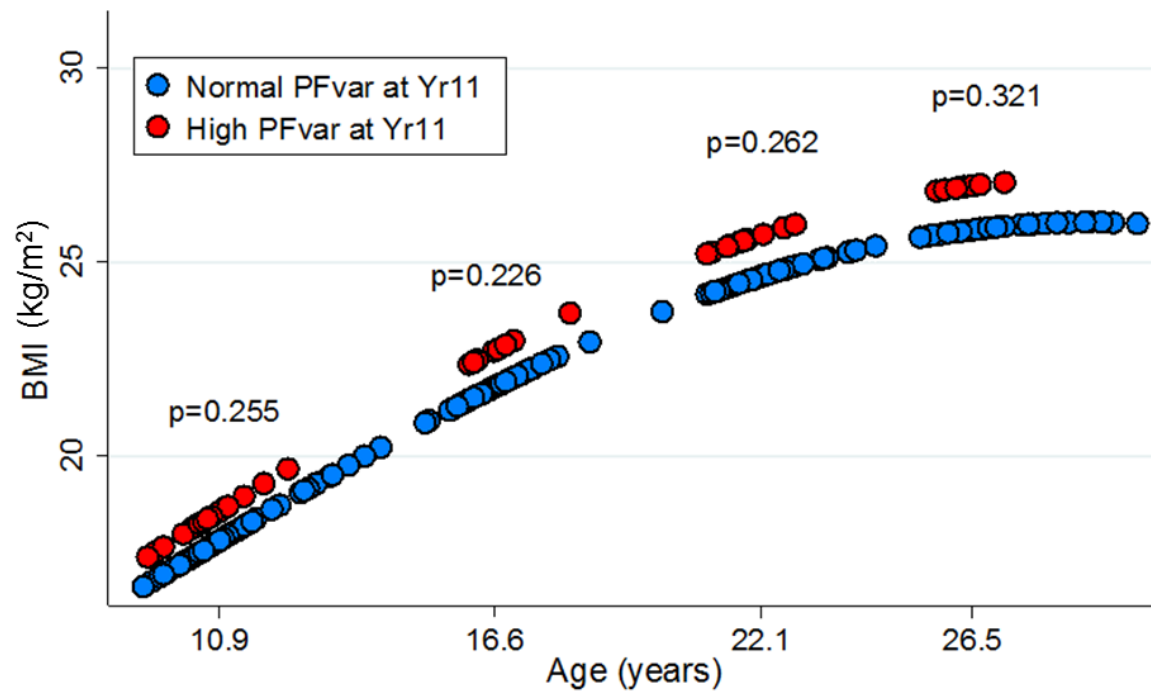
Abbreviations: PFvar=peak expiratory flow variability; MET= metabolic equivalents of task;

95%CI=95% confidence interval

* Metabolic Equivalents of Task (METs) were used as an ordinal variable at each survey where the first category was 0 MET hours/week, the second category was between 1 and 40 MET hours/week, and the third category was > 40 MET hours/week (see text).

[§] Reference category: both non-Hispanic White parents.





Online Repository

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METHODS

The Tucson Children's Respiratory Study (CRS) is a longitudinal cohort study involving 1,246 children enrolled at birth between May 1980 and October 1984¹. Questionnaires on participants' respiratory symptoms were completed by their parents at age 11 [Yr11: mean (SD) 10.7 (0.5) yr] and 16 [Yr16: mean (SD) 16.6 (0.6) yr] and by participants themselves at age 22 [Yr22: mean (SD) 22.1 (0.9) yr] and 26 [Yr26: mean (SD) 26.5 (0.9) yr]. At each survey, current asthma was defined as a positive report of asthma diagnosed by a physician with at least one asthma attack or wheezing episode during the previous year. Information on sport-related physical activity during the previous year was also collected at each survey using the questions: "Is this child a member of a sports team?" at Yr11; "Does this child participate in sports?" at Yr16; and "During the past year, have you exercised regularly?" at Yr22 and Yr26. Metabolic equivalents of task (METs) were calculated according to Ainsworth and colleagues² using the questions "If yes, in which sports? (hours per week)" at Yr11 and Yr16 and "Which type of exercise have you done regularly? (hours per week)" at Yr22 and Yr26. METs were categorized into 3 levels, namely 1 "0 MET hours per week", 2 "1-40 MET hours per week", and 3 ">40 MET hours per week".

Skin prick tests were performed at each survey. For the sake of consistency, in this study we considered only the six aeroallergens that were tested in all four surveys: Bermuda grass, careless weed, olive, mesquite, mulberry, and *Alternaria alternata* (Hollister-Stier Laboratories, Everett, Washington, DC).

Histamine and a negative control consisting of 50% glycerin were also applied. Tests were read at 20 minutes and the size of the wheal elicited by each allergen was recorded as the longest diameter plus the perpendicular diameter (in mm). Wheal sizes of 3 mm or greater, after subtracting the negative control, were considered positive. A subject was considered atopic if he/she had a positive skin test reaction to at least one aeroallergen.

Study nurses used beam balance scales at each survey to measure weight (Health-o-meter; Continental Scale Corp., Chicago, IL). Height was measured with the subject barefoot and erect against a vertical backboard or wall-mounted scale (Accustat-Stadiometer; Genentech, San Francisco, CA). Self-reported weight and height were also available from the questionnaires. Body mass index (BMI) was calculated as weight (Kg)/square of height (m²). Subjects were considered to be “obese” if their BMI was $\geq 95^{\text{th}}$ percentile of CDC 2000 U.S. sex and age standardized values up to the age of 17 yr³ or if their BMI was $\geq 30 \text{ Kg/m}^2$ over age 17 yr⁴. Subjects were considered to be “overweight/obese” if their BMI was $\geq 85^{\text{th}}$ percentile of CDC 2000 U.S. sex and age standardized values up to the age of 17 yr³ or if their BMI was $\geq 25 \text{ Kg/m}^2$ over age 17 yr⁴.

At a mean age of 10.8 yr subjects were trained by study nurses on the use of a home peak expiratory flow (PEF) meter (“Mini-Wright”, Clements Clarke International, Harlow, Essex, UK) and parents were asked to record on a diary the best of three attempts of their children in the morning, in the afternoon, and before going to bed at night. PEF data were collected for 1 week. To avoid the “learning effect” on PEF measurements, as previously reported⁵, measures from the first morning of the PEF recording period were eliminated from the analysis. Only subjects who recorded PEF measurements at least twice a day for ≥ 4 days (after exclusion of the first morning of the recording period) were included in the analysis^{5,6}. The amplitude percent mean^{5,7} was chosen as the PFvar index and defined as:

$$\text{PFvar} = \frac{\sum (\text{maximum daily PEF} - \text{minimum daily PEF}) / \text{mean daily PEF} \times 100}{\text{number of days in the period}}$$

Consistent with our previous report, high PFvar at Yr11 was defined as a PFvar value greater than or equal to 16.6% (i.e., above the 90th percentile of a healthy reference subgroup of subjects who were skin test negative, had never wheezed, nor had been diagnosed as having asthma)⁵.

The potential confounding effects of parental education, ethnicity, and smoke exposure were also tested. Maternal and paternal education was assessed at child's enrollment in the CRS and categorized into "≥ 12 years" and "≤ 12 years". Ethnicity was categorized based on the ethnicity of parents ("both parents non-Hispanic White", "at least one Hispanic White parent", or "other"). For smoke exposure, four combination groups were generated based on parental smoking at child's birth and active participant smoking between Yr16 and Yr26, as previously reported⁸: "No parental smoking/No active smoking", "No parental smoking/Yes active smoking", "Yes parental smoking/No active smoking", and "Yes parental smoking/Yes active smoking".

This study was approved by the Human Subjects Committee at the University of Arizona, and informed consent was obtained from the parents before age 18 and, subsequently, from the participants themselves.

Statistical Analysis

BMI and PFvar values were logarithmically transformed (base 10) to obtain a normal distribution. Student's t-test and the χ^2 test were used for comparisons of means and proportions, respectively. Linear regression was used in the univariate analysis to assess the relation between PFvar at Yr11 and BMI at Yr11, Yr16, Yr22, and Yr26, respectively. In order to adjust for the intra-subject serial correlation of repeated observations, generalized estimating equations (GEE) were used to assess the association between dichotomous PFvar at Yr11 and the categorical variable indicating obese subjects at each of the four surveys⁹ and random effects models were used for all

the multivariate longitudinal analyses with log-transformed BMI as the continuous dependent variable⁹. In the random effects models age was centered to the youngest child included at age 11. Linear contrast was used to estimate survey specific effects. Stata version 14.0 was used for analysis. Potential confounders of the relationship between PFvar and BMI were included in the models *a priori*. Statistical significance was tested at a two-sided alpha level of 0.05.

RESULTS

PEF variability information at Yr11 was collected for 600 children and all children had one or more BMI measurement. BMI was assessed by the study nurses at Yr11 (n=599), Yr16 (n=448), Yr22 (n=397), and Yr26 (n=336). Excellent correlation was found between BMI assessed by the study nurses and questionnaire reported BMI (Spearman rho 0.97 at Yr11, 0.96 at Yr16, 0.98 at Yr22, and 0.95 at Yr26). For this reason, to minimize the potential selection bias due to missing information at follow up, questionnaire reported BMI at Yr16, Yr22, and Yr26 was used for those subjects for whom BMI assessed by the study nurses was missing at those surveys. Thus, among the 600 children with PFvar information at Yr11, the final number of subjects with subsequent BMI information was 500 at Yr16, 485 at Yr22, and 453 at Yr26.

The characteristics of the study subjects at each survey are reported in Table 1. At Yr11, as compared with participants who were included in the present study, those who were excluded because they had missing information on BMI or PFvar were slightly older, more physically active, and had a higher proportion of non-Hispanic White parents (Table E1). In contrast, no significant differences were found in sex, asthma, atopy, and parental education.

Geometric mean (95%CI) BMI values at each survey for the subjects included in the study are also reported in Table 1. The proportion of overweight/obese subjects was 27.4% at Yr11,

23.2% at Yr16, 39.2% at Yr22, and 50.8% at Yr26. At Yr11 the geometric mean (95%CI) PFvar was 7.6 (7.3, 8.0)%, range 0.7-41.9%, and 62 children (10.3%) had a high PFvar.

In univariate analyses, a significant linear correlation was found between log-transformed PFvar at Yr11 and log-transformed BMI at Yr11 ($r=0.10$, $p=0.015$), Yr16 ($r=0.14$, $p=0.001$), Yr22 ($r=0.14$, $p=0.002$), and Yr26 ($r=0.11$, $p=0.019$). In addition, as compared with subjects with normal PFvar, those with high PFvar had higher BMI at Yr11 ($p=0.037$), Yr16 ($p=0.0001$), Yr22 ($p=0.0003$), and Yr26 ($p=0.068$). PFvar at Yr11 tended to have a stronger association with subsequent (Yr16, Yr22, and Yr26) than with concomitant (Yr11) BMI. Consistent with this scenario, Figure E1 shows that, as compared with participants with normal PFvar, those with high PFvar at Yr11 were more likely to be obese at Yr16 [RR (95% CI) from GEE models: 2.00 (1.17, 3.39)], Yr22 [2.31 (1.53, 3.48)], and Yr26 [1.77 (1.23, 2.56)], but not at Yr11 [1.38 (0.75, 2.54)]. When we looked for a possible association between high PFvar at Yr11 and obesity earlier in childhood, we found that, similarly to Yr11, at age 6 (mean 6.3 yr) children with high PFvar at Yr11 were not more likely to be obese than those with low PFvar at Yr11 [RR (95% CI) 1.55 (0.73, 3.31), $p=0.308$].

In random effects models that used log-transformed BMI at Yr11, Yr16, Yr22, and Yr26 as the dependent variable, after adjusting for sex, maternal and paternal education, and ethnicity as fixed covariates and for age, age squared, concurrent asthma, atopy, and METs at each survey as time-dependent covariates, we found subjects with high PFvar to have only marginally increased BMI at age 11 but significantly higher BMI at all other ages than subjects with normal PFvar, with the largest differences achieved by age 26 (Figure 2A). Likelihood ratio tests indicated that the best fitting model (Table 2) included both age and age squared terms, consistent with the previously described deceleration of BMI increase from childhood to young adult life. The best fitting model also included an interaction term between high PFvar and age ($p<0.001$), indicating that after adjustment for covariates high PFvar at Yr11 was strongly associated with a steeper increase

of BMI over time. An additional interaction term between high PFvar and age squared was also tested, found non-significant, and therefore removed from the final model. After further adjustment of the model for smoke exposure, results remained virtually unchanged (data not shown). Similarly, results did not change when the analysis was repeated using only BMI values from direct measurements by the study nurses.

Of note, when random effects models were stratified by sex we found notable differences in the association between PFvar and BMI increase between females and males (Table 3 and Figures 2B and 2C). The interaction between high PFvar and age was highly significant in females ($p < 0.001$) but not in males ($p = 0.968$), showing that the effect of high PFvar on the subsequent BMI increase was only present in the former group. Indeed, among males no association was seen between high PFvar and BMI levels at any age. These results were confirmed after restricting analyses for subjects who did not have current asthma and were not overweight/obese at Yr11 (196 female and 157 male). Once again, the interaction between high PFvar and age was significant in females ($p = 0.039$), but not in males ($p = 0.935$).

DISCUSSION

In this study we found high PFvar at age 11 to predict a steeper subsequent BMI increase up to young adult life independent of multiple covariates, including parental education, level of physical activity, and current asthma at age 11. By age 26, participants who had high PFvar in childhood were nearly twice as likely to be obese as were their peers who had normal PFvar in childhood. Interestingly, the effects of high PFvar were much stronger on subsequent than concomitant levels of BMI suggesting that our findings are very unlikely to be explained by concomitant effects of obesity on airway lability.

The prevalence rates of obesity and asthma have increased dramatically in many countries in recent decades¹⁰ and several cross-sectional studies have shown an association between these conditions, both in children^{11,12} and adults^{13,14}. In addition, longitudinal studies have found that excess weight increases the risk of subsequent asthma development in childhood¹⁵⁻¹⁷ as well as in adult life¹⁸⁻²⁰. Meta-analyses have confirmed these longitudinal relations. In children, the combined results from 6 prospective studies showed that the combined risk ratio (RR) of obesity for subsequent physician-diagnosed incident asthma at least one year after BMI assessment was significant in both boys (RR = 1.40; 95% CI = 1.01, 1.93) and girls (RR = 1.53; 95% CI = 1.09, 2.14)²¹. A meta-analysis that combined the results from 9 studies on the effects of high birth weight on subsequent asthma found a pooled RR of 1.2 (95% CI 1.1 to 1.3) in a total of 110,402 children²². In adults, a meta-analysis of 7 longitudinal studies including a total of 333,102 subjects found that a BMI ≥ 25 Kg/m² conferred an odds ratio (OR) of 1.51 (95% confidence interval, CI, 1.27-1.80) for incident asthma when compared with normal weight, and this effect showed a dose-response relationship²³.

Several mechanisms have been proposed to explain the link between obesity and asthma²⁴. Mechanical factors, such as reduced functional residual capacity and low tidal volume with subsequent increase in airway smooth muscle stiffness and bronchial hyperreactivity, have been shown to play a possible role^{24,25}. The increase in proinflammatory adipokines, such as leptin, eotaxin, interleukin-6, tumor necrosis factor- α , etc., and the decrease in adiponectin and its anti-inflammatory effects have been reported to underlie the state of chronic systemic inflammation present in obesity and have been suggested to be also involved in the inflammation present in asthma^{24,26}. Finally, comorbid conditions, such as dyslipidemia, gastroesophageal reflux, type 2 diabetes, or sleep-disordered breathing, may also play a role in the relationship between obesity and asthma²⁴.

The above postulated mechanisms are largely based on the assumption that obesity is causally linked to asthma risk. However, a recent follow up of subjects with asthma during childhood in two separate cohorts suggested that the inverse association may also be true: children with asthma are at increased risk of subsequently developing obesity²⁷. It is thus possible that the association between asthma and obesity may be bidirectional, with different factors explaining the association between obesity and asthma as compared with those explaining that between asthma and obesity. Alternatively, a more parsimonious explanation could be that the link between these conditions is due to shared factors that preexist both and are expressed as either asthma or obesity at different times during the lifetime as a function of other, unknown determinants. In this framework, obesity and asthma are known to share common genetic mechanisms^{28,29}. In a study on 1001 monozygotic and 383 dizygotic same-sex twin pairs, 8% of the genetic component of obesity was shown to be shared with asthma³⁰. In line with this scenario, a ~0.45 Mb genomic inversion at 16p11.2 (which includes multiple potential asthma and obesity candidate genes) was recently associated with the risk for the joint occurrence of asthma and obesity in five independent studies, supporting the existence of a possible common genetic predisposition to both conditions³¹. Developmental and early life factors, such as prenatal exposure to specific nutrients and patterns of colonization of the infant gut, have been also suggested as affecting the development of both obesity and asthma^{28,32}. We reasoned that, if such common factors do exist, they could cause both an alteration in the regulation of airway tone and a greater tendency to gain weight during the growing years and that the asthma-related phenotype could precede the obesity phenotype even in subjects without asthma. Consistently, in the present study high PFvar at age 11 predicted BMI increase and development of obesity by age 26 independent of asthma diagnosis and other confounders, and these effects were confirmed when repeating the analysis in subjects who were neither obese nor asthmatic at age 11.

PFvar is considered an important measurement in screening for asthma in population-based studies³³ and is recommended by asthma guidelines as a possible tool for the diagnosis and management of the disease³⁴. However, we have previously shown that PFvar is present in the non-atopic toddlers long after wheezing symptoms have ceased⁵ and it may represent an indicator of airway lability only partly related to asthma symptoms. These observations, together with the finding that high PFvar in childhood was associated with a steeper BMI increase by age 26 independent of asthma and even after restricting analyses to non-asthmatics, suggest it is unlikely that respiratory symptoms and the consequent reduction in physical activity may be responsible for the weight gain among subjects with high PFvar. In addition, to reduce potential confounding by physical activity, we also included METs (based on sport-related physical activity at the four surveys) as an independent variable in longitudinal multivariate analysis and confirmed the relationship between PFvar and subsequent BMI in these models. However, it should be noted that our questionnaires focused on sports participation at Yr11 and Yr16, and on regular exercise activity at Yr22 and Yr26, and were not designed to thoroughly investigate the complex relationship between sedentary lifestyle, obesity, and asthma.

A limitation of this study is the potential selection bias of the participants, since information on PFvar at Yr11 and subsequent BMI was not available for the whole population. However, we found that at Yr11 those who were excluded because of missing information on PEF were slightly older, more physically active, and had a higher proportion of non-Hispanic white parents as compared with participants who were included in the present study, but were not significantly different as long as sex, asthma, atopy, and parental education were concerned.

We also attempted to minimize the potential limitation due to missing BMI information after Yr11. Since excellent correlation was found between BMI assessed by the study nurses and self-reported BMI in the questionnaires, self-reported BMI information at Yr16, Yr22, and Yr26 was

used for those subjects for whom BMI assessed by the study nurses was missing at those surveys, thus largely decreasing the number of subjects with missing BMI information.

Other important potential limitations are due to the nature itself of PEF measurements, that are by design effort-dependent, while PEF devices offer no objective assurance as to the effort of the maneuver. However, the effect of these potential limitations would be an increase in the “background noise” and a decrease in the detectable effect of PFvar on subsequent BMI. Also, if the relationship between PFvar and BMI were simply explained by the fact that subjects with a higher BMI are de-conditioned and have a lower lung function, one might expect a better correlation between high PFvar and elevated BMI at all surveys, which was not the case in our study. Furthermore, to ensure that only PEF measurements with a good adherence were analyzed, only subjects who recorded PEF measurements at least twice a day for ≥ 4 days (after exclusion of the first morning of the recording period) were included in the analysis. Another limitation is that PFvar was measured during only one 1-week at Yr11 instead of having repeated measurements over the period of the study.

Although our finding that high PFvar preceded BMI gain applies to the entire CRS study population, we found indication that this association is stronger in females than males, among whom it did not reach statistical significance. The literature is not always consistent in showing differences by sex in the relation of asthma and obesity³⁵. While in adults a stronger association between overweight/obesity and asthma is generally found in females than in males²⁹, in children this association has been reported both in females and in males^{16,17,36,37} and a meta-analysis of six studies found a larger effect of overweight/obesity on subsequent asthma incidence in boys than in girls³⁸. In our population we have previously shown that females who became overweight or obese between 6 and 11 years of age were 7 times more likely to develop subsequent asthma symptoms by age 13 than females who were not overweight or obese¹⁵. We have also shown a

higher prevalence of abnormal PFvar in girls who became overweight or obese during the school years as compared with those whose BMI level did not change or decreased during the same time interval¹⁵. These girls were also significantly more likely to show a positive response to albuterol than those who did not become overweight or obese during the same period, thus suggesting the presence of an abnormal regulation of airway tone. The reasons why the link between high PFvar and steeper increase in BMI may be stronger in girls than boys remain unclear, although hormonal differences are likely to play a role^{35,39}.

In conclusion, we found peak flow variability in childhood to be a significant predictor of subsequent BMI increase by age 26, particularly in females, suggesting that the relationship between obesity and asthma-related phenotypes may not be unidirectional. Developmental and genetic factors common to asthma and obesity may explain at least in part the association between these two phenotypes.

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FIGURE LEGENDS

Fig. E1 - Proportions of obese children at the four surveys by peak flow variability (PFvar) at age 11. P-values related to group differences at each time point were tested using linear contrast from a longitudinal GEE univariate analyses with PFvar at age 11 as the independent variable and obesity at age 11, 16, 22 and 26 as the dependent variable.

Fig. E2 - Linear prediction of base 10 log-transformed body mass index (BMI) vs age for subjects with high (red circles) and normal (blue circles) PFvar at age 11. Linear predictions were calculated from random effects models adjusted for sex, maternal and paternal education, and ethnicity as fixed effects and current asthma, atopy, and Metabolic Equivalents of Task (METs) at each survey as time-dependent covariates in the whole study group. P-values related to group differences at each time point were tested using linear contrast.

Table E1 - Characteristics of the study subjects at age 11 (for proportions, the actual numbers are shown in parentheses)*.

	Yr11	
	Included <i>n</i> = 600	Not Included <i>n</i> = 356
Age, yr, mean (SD)	10.7 (0.5)	11.1 (0.8) §
% Male	48.2 (289/600)	49.7 (177/356)
% Current Asthma	17.6 (104/592)	13.2 (46/349)
% Atopy	54.7 (327/598)	57.3 (63/110)
% Current Physical Activity MET hr/wk:	51.3 (307/599)	57.9 (206/356) †
% 0	48.8 (292/598)	42.3 (150/355) †
% 1-40	25.4 (152/598)	23.9 (85/355)
% >40	25.8 (154/598)	33.8 (120/355)
% Maternal Education ≤12yrs	28.9 (173/599)	25.6 (91/356)
% Paternal Education ≤12yrs	26.2 (154/588)	23.1 (81/351)
Parental Ethnicity:		
% Non-Hispanic White	60.8 (365/600)	70.8 (252/356) †
% ≥1 Hispanic White	25.8 (155/600)	16.0 (57/356)
% Other Ethnicity	13.3 (80/600)	13.2 (47/356)
BMI, kg/m², GM (95%CI)	18.6 (18.3, 18.9)	18.3 (18.0, 18.7)
% Overweight/Obese	27.4 (164/599)	24.6 (75/305)
% Obese	12.2 (73/599)	10.2 (31/305)

Abbreviations: SD=standard deviation; MET= metabolic equivalents of task; BMI=body mass index; GM=geometric mean; 95%CI=95% confidence interval

* Totals are not the same for all individual characteristics because information is missing for some subjects.

§ $p < 0.001$ by t-test vs study subjects at same age.

|| $0.1 > p > 0.05$ by Chi² test vs study subjects at same age.

† $p < 0.05$ by Chi² test vs study subjects at same age.

Table E2 - Characteristics of the study subjects at age 11 (Yr11), age 16 (Yr16), age 22 (Yr22), and age 26 (Yr26) (for proportions, the actual numbers are shown in parentheses)*.

	Yr11 <i>n</i> = 600	Yr16 <i>n</i> = 500	Yr22 <i>n</i> = 485	Yr26 <i>n</i> = 453
Age, yr, mean (SD)	10.7 (0.5)	16.6 (0.6)	22.1 (0.9)	26.5 (0.9)
% Male	48.2 (289/600)	49.2 (246/500)	46.6 (226/485)	46.1 (209/453)
% Current Asthma	17.6 (104/592)	19.4 (95/489)	18.7 (90/482)	20.9 (92/445)
% Atopy	54.7 (327/598)	72.0 (317/440)	72.6 (278/383)	72.9 (240/329)
% Current Physical Activity	51.3 (307/599)	57.9 (287/496)	64.0 (307/480)	66.6 (297/446)
METs hr/wk:				
% 0	48.8 (292/598)	40.8 (197/483)	36.2 (173/478)	34.5 (147/426)
% 1-40	25.4 (152/598)	17.6 (85/483)	24.7 (118/478)	32.4 (138/426)
% >40	25.8 (154/598)	41.6 (201/483)	39.1 (187/478)	33.1 (141/426)
% Maternal Education ≤12yrs	28.9 (173/599)	24.6 (123/499)	25.4 (123/485)	25.0 (113/452)
% Paternal Education ≤12yrs	26.2 (154/588)	23.4 (115/491)	25.4 (121/477)	23.1 (103/446)
Parental Ethnicity:				
% Non-Hispanic White	60.8 (365/600)	62.4 (312/500)	63.1 (306/485)	64.7 (293/453)
% ≥1 Hispanic White	25.8 (155/600)	24.6 (123/500)	24.7 (120/485)	23.6 (107/453)
% Other Ethnicity	13.3 (80/600)	13.0 (65/500)	12.2 (59/485)	11.7 (53/453)
BMI, kg/m², GM (95%CI)	18.6 (18.3, 18.9)	22.5 (22.1, 22.9)	24.9 (24.4, 25.4)	26.2 (25.7, 26.8)
% Overweight/Obese	27.4 (164/599)	23.2 (116/500)	39.2 (190/485)	50.8 (230/453)
% Obese	12.2 (73/599)	12.4 (62/500)	17.5 (85/485)	24.1 (109/453)

Abbreviations: SD=standard deviation; METs= metabolic equivalents of task; BMI=body mass index; GM=geometric mean; 95%CI=95% confidence interval

* Totals are not the same for all individual characteristics because information is missing for some subjects.

§ $p < 0.001$ by t-test vs study subjects at same age.

|| $0.1 > p > 0.05$ by Chi² test vs study subjects at same age.

† $p < 0.05$ by Chi² test vs study subjects at same age.

Table E3 - Longitudinal analysis by random effects model of base 10 log-transformed BMI at ages 11, 16, 22, and 26 as the dependent variable and potential confounders at the four surveys (n=584, obs=1670). Yr11 age was centered at the youngest age, 9.2 years, to facilitate interpretation of the main effect coefficient of PFvar.

	<i>Coefficient</i>	<i>95% CI</i>	<i>p</i>
High PFvar at Yr11	0.016	-0.008, 0.041	0.195
Age	0.019	0.018, 0.021	<0.001
Age²	-0.0005	-0.0006, -0.0004	<0.001
High PFvar x Age	0.002	0.0005, 0.003	0.008
Male Sex	0.002	-0.012, 0.016	0.784
Concurrent Asthma	0.010	-0.0007, 0.019	0.035
Concurrent Atopy	-0.005	-0.013, 0.003	0.220
Concurrent METs[*]	-0.003	-0.007, -0.0001	0.041
Maternal Education ≤12yrs	0.011	-0.006, 0.0297	0.218
Paternal Education ≤12yrs	0.023	0.005, 0.041	0.012
≥ 1 Hispanic Parent[§]	0.014	-0.003, 0.030	0.105
Other Ethnicity[§]	0.015	-0.007, 0.037	0.173

Abbreviations: PFvar=peak expiratory flow variability; MET= metabolic equivalents of task;

95%CI=95% confidence interval

* Metabolic Equivalents of Task (METs) were used as an ordinal variable at each survey where the first category was 0 MET hours/week, the second category was between 1 and 40 MET hours/week, and the third category was > 40 MET hours/week (see text).

§ Reference category: both non-Hispanic White parents.

