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Airway obstruction worsens in young adults with asthma who become obese

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Abstract

Background—Few studies have examined how developing obesity in early adulthood affects the course of asthma.

Objective—We analyzed lung function and asthma impairment and risk among non-obese children with asthma, comparing those who were obese in young adulthood to those who remained non-obese.

Methods—Post-hoc analysis of 771 subjects with mild-moderate asthma who were not obese (pediatric definition, body mass index (BMI) <95th percentile) when enrolled in the Childhood Asthma Management Program at ages 5–12 years. Subjects were then followed to age 20 years. For visits at ages 20 years, spirometry values as percent predicted and recent asthma symptom scores and prednisone exposure were compared between 579 subjects who were non-obese at all visits and 151 who obese (adult definition of BMI ≥30 kg/m²) on at least one visit (median number of visits when obese = 4, IQR 2–7).

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Results—Compared to participants who were non-obese (BMI 23.4 ± 2.6 kg/m²), those who became obese (BMI 31.5 ± 3.8 kg/m²) had significant decreases in FEV₁/FVC ($p < 0.0003$) and FEV₁ ($p = 0.001$), without differences in FVC ($p = 0.15$) during visits at ages 20 years. For each unit increase of BMI, FEV₁ percent predicted decreased by 0.29 ($p = 0.0009$). The relationship between BMI and lung function was not confounded by sex or BMI at baseline. Asthma impairment (symptom scores) and risk (prednisone use) did not differ between the two groups.

Conclusion—Becoming obese in early adulthood was associated with increased airway obstruction, without impact on asthma impairment or risk.

Keywords

Childhood asthma; childhood obesity; obese asthma; pulmonary function

Introduction

Both obesity and asthma are increasing in incidence and prevalence in the United States. Numerous cross sectional studies have demonstrated higher rates of asthma in obese individuals compared to normal weight controls for both children and adults (reviewed in^{1,2,3,4}). Longitudinal studies^{5,6,7} have found that development of obesity in school age years is associated with greater incident asthma during adolescence. Several groups have found that among individuals with asthma, those who are obese have worse control, greater need for albuterol and oral corticosteroids, are more often hospitalized, have a decreased response to inhaled corticosteroids, and have lower quality of life^{8,9,10,11,12}. Furthermore, weight gain worsens asthma symptoms among those with severe or difficult-to-treat asthma¹³, and weight loss improves both asthma control and lung function^{14,15,16}. However, obesity-related dyspnea is often misinterpreted as an asthma symptom, indicating that obesity can produce symptoms without affecting asthma^{17,18}.

Cross-sectional studies have assessed the effects of obesity in youth on specific aspects of pulmonary function. A cross sectional analysis of children with asthma ages 5–12 years enrolled in the Childhood Asthma Management Program (CAMP) found that increased body mass index (BMI), assessed as a continuous variable, was associated with increased FVC and FEV₁, but decreased FEV₁/FVC ratio¹⁹. There were no associations between increased BMI and clinical symptoms¹⁹. Other cross-section studies have confirmed the finding in children with asthma that increased BMI is associated with decreased FEV₁/FVC, with the findings similar in white, African American, and Hispanic groups²⁰ and in those with asthma and without asthma and in both sexes²¹.

Longitudinal studies examining the impact of weight gain on asthma are limited. A study of adults with asthma over 7–11 years of follow-up, focusing on the effects of weight gain, not the development of obesity, on lung function²² found that increases in BMI were related to decrements in FEV₁ and FEV₁/FVC. These findings were most prominent in individuals who had no airway obstruction at baseline. However, no longitudinal studies have been done in children or young adults and no longitudinal study has focused on the outcome of obesity.

This study examined children ages 5–12 years, who were not obese at entry in CAMP and were followed over an average of 16 years with frequent follow-up visits with assessment of lung function and collection of height, weight, and measures of asthma impairment and risk. During young adulthood, 25% had become obese. We hypothesized that those who had become obese in young adulthood would have greater airway obstruction than those who remained non-obese.

Methods

Study and subjects

The CAMP trial was a 4–6 year long multicenter randomized controlled trial measuring the effects of budesonide, nedocromil, and a placebo on asthma outcomes in 1041 participants 5–12 years of age. The protocol and primary outcomes have been published previously^{23,24}. During the trial and 12 years of post-trial follow-up, visits occurred every 4–12 months. Visits consisted of height and weight measurements, spirometry, and questionnaires to assess asthma symptoms, health care utilization, and prednisone courses, all standardized across the eight CAMP clinical centers²³ (see Online Supplement for clinical centers). CAMP procedures were approved by Institutional Review Boards at each of the clinical centers and for the CAMP Data Coordinating Center. Written informed consent was obtained from all participants.

Data were available on 897 participants followed for 16.2 ± 1.1 years (9–17.8 years) with age at final visits 20 years or older (24.7 ± 2.3 , range 20 to 30 years). Baseline BMI percentiles were calculated from CDC growth charts²⁵. We excluded 126 participants who were obese (by the pediatric definition BMI $\geq 95^{\text{th}}$ percentile²⁶) at enrollment. We evaluated spirometry measures and measures of asthma impairment and risk by obesity status during follow up visits when participants were 20 years or older. Obesity during the visits was defined using the adult definition BMI $\geq 30 \text{ kg/m}^2$ ^{26,27}

Pulmonary Function

Pulmonary function was determined by spirometry both before and after bronchodilator (two 90- μg actuations of a pressurized metered-dose inhaler). Measures examined were percent of predicted forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC . Baseline percent predicted spirometry values for were determined using Wang et al.²⁸ for those ages 6 and 7 years old and Hankinson et al.²⁹ for those >7 years old. Airway hyper responsiveness was defined as the concentration of methacholine that caused a decrease of 20% from baseline FEV_1 ($\text{PC}_{20}\text{-FEV}_1$)³⁰.

Asthma impairment and risk

Impairment—Asthma symptoms since the last visit were assessed at each visit using the American Thoracic Society's Division of Lung Diseases questionnaire for children (ATS-DLD-78-C). For this analysis, answers to questions about wheezing and shortness of breath after playing hard or exercise as “yes” or “no” were used.

Risk—Participants were asked about their use of prednisone since the last visit at each visit.

Statistical analysis

The association between obesity status during young adulthood and lung function measures over time was assessed in this analysis. Baseline characteristics were evaluated across two groups based on obesity status during young adulthood: a) non-obese group: not obese at enrollment and at all follow-up visits at age 20 or greater, or b) became-obese group: not obese at enrollment, but were obese during at least one follow up visit at age 20 or greater. Unadjusted comparisons were assessed using t tests for measured variables or Fisher's exact tests for categorical variables.

The relationship between pulmonary function and obesity status at each visit during young adulthood was conducted using linear regression. Logistic regression was used to assess the relationship between wheeze without cold, shortness of breath while playing, prednisone course since last visit, and obesity status at the visit. All models used generalized estimating equations (GEE) to account for within-participant correlation.

Multivariable regression analyses included baseline covariates race/ethnicity, sex, age, log IgE, BMI percentile, and spirometry (in models where spirometry was the outcome measure) and time-varying covariates ICS use and wheeze without a cold (when not also the outcome measure). Covariate inclusion was based on 1) significance in univariate analyses, or b) backward stepwise selection ($P=0.05$ for removal). Characteristics analyzed but were not related to outcome measures at the $P=0.05$ level of significance were: family income $\leq 50k$ at baseline, parent education $>$ high school at baseline, baseline measurements of water damage to home ever, presence of mold/mildew in home over the past year, furry/feathered pets in the home, log eosinophil count at baseline, asthma severity at baseline, randomization clinic, presence of positive skin test at baseline, shortness of breath while playing at each visit, prednisone course administered since previous visit, and ICS use prior to enrollment. Unadjusted models included a covariate for spirometry at baseline, when spirometry was the outcome variable.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

On entry into the CAMP trial, there were no significant differences between the non-obese and obese groups in regards to gender, family income, parental education, pulmonary function measures of pre-bronchodilator spirometry and airway responsiveness, atopy indicators, treatment group, environmental exposures, overall asthma severity, or prior ICS use (Table 1). The group that was obese in young adulthood had a greater percentage of minorities, was older, and had a greater BMI percentile at randomization (Table 1).

Ages at last visits in the non-obese and obese groups were 24.5 ± 2.3 and 25.1 ± 2.2 , with numbers of visits at ages ≥ 20 years 6.5 ± 3.3 and 7.5 ± 3.2 , respectively. The median number of visits when an individual met criteria for obesity was 4 (IQR 2–7), with the proportion of visits of obese subjects where obesity was present was 66.7% (IQR 32.1–100%). Mean BMI values for all visits at ages ≥ 20 years were 23.4 ± 2.6 and 31.5 ± 3.8 kg/m² for the non-obese and obese groups, respectively.

Unadjusted and adjusted linear regression models of pulmonary function by obesity status at each visit when a participant was ≥ 20 years of age are shown in Table 2. The differences in pre-bronchodilator percent predicted values for FEV₁ and FEV₁/FVC by obesity status at the visit are statistically significant, whereas the FVC does not differ. For adjusted analyses, obesity at the visits was associated with a reduction of 3.06 (p=0.001) in percent predicted FEV₁ and 2.24 (p=0.0009) in percent predicted FEV₁/FVC. Similar results were obtained for spirometry values obtained post-bronchodilator (Table 2). The adjusted means for spirometry measures, both pre- and post-bronchodilator, by obesity status at each visit when a participant was ≥ 20 years of age are shown in Table 3.

Unadjusted and adjusted linear regression models of measures of asthma impairment (wheeze without colds and shortness of breath while playing) and risk (prednisone courses), at each visit did not differ by obesity status at the visit (Table 2).

Unadjusted and adjusted linear regression models of pulmonary function measures by BMI as a continuous variable at each visit when the participant was ≥ 20 years of age are shown in Table 4. For each unit increase in BMI, pre-bronchodilator percent predicted values for FEV₁ decreased by 0.29 (p=0.0009) and FEV₁/FVC decreased by 0.31 (p=<0.0001), but there was no change in FVC (p=0.94). Similar results were obtained for spirometry values obtained post-bronchodilator (Table 4). Unadjusted and adjusted linear regression models of measures of asthma impairment (wheeze without colds and shortness of breath while playing) and risk (prednisone courses) at each visit also not differ by BMI as a continuous variable at the visit (Table 4).

Discussion

Our findings show that children with mild to moderate asthma who were not obese during ages 5–12 years at entry into the CAMP trial and subsequently became obese in early adulthood had greater airway obstruction compared to those who remained non-obese. Both FEV₁ and FEV₁/FVC were significantly lower in the obese group compared to those in the non-obese group, whereas FVC did not differ by obesity status. These findings were present when the spirometry values were analyzed by measures at each visit when ≥ 20 years of age, and for values adjusted for BMI at each visit.

The effects of increased BMI on lung function observed in our cohort of children with asthma are similar to those observed by Marcon et al.²² who found in adults aged 28–43 years of age that weight gain was associated with declines in FEV₁ and FEV₁/FVC independent of baseline BMI over a 6–11 year follow-up²². Importantly, the development of obesity in 25% of children in the CAMP cohort cannot be explained by them having worse asthma than those who were not obese. First, lung function at baseline was not different between the two groups, either by spirometry or airway responsiveness to methacholine. Second, the global assessment of severity as mild or moderate at baseline did not differ between groups. Finally, asthma impairment and risk did not differ between the groups during the visits when spirometry was measured at ages ≥ 20 years.

The finding of no increases in asthma symptoms or prednisone use in the became-obese group compared to the non-obese group is similar to the findings by Tantisira et al. that increasing BMI in a cross sectional study was not associated with symptoms¹⁹ and Peters et al.³¹ who found that there were no significant differences in asthma severity by BMI categories. However the findings in children and young adults are different than in older adults, where there were adverse effect of obesity on asthma symptoms and level of control¹⁰. It is possible that the levels of BMI present in our cohort, while significantly into the abnormal range, were not yet sufficient to affect symptoms.

Several studies have not found an effect of sex on the association between obesity and asthma severity and control in either children⁹ or adults¹⁰. Recently Borrell et al. found that worse asthma control was uniformly associated with increased BMI in boys, but the association in girls varied by race and ethnicity¹¹. In our cohort, there was not an effect of sex in the development of obesity during the follow-up or in the effect of obesity in the development of lung function changes. In addition, there was no effect of race/ethnicity in the development of the lung function differences.

The increase in airway obstruction in individuals with asthma who were obese in young adulthood is in contrast to the traditional notion that obesity causes primarily a restrictive ventilatory defect, with decreases in compliance of the lung and chest wall and increase in airway and respiratory system resistance³². In severe obesity, i.e., BMI >45 kg/m², the restrictive defect is also evidenced by a simultaneous decrease in both FEV₁ and FVC by 20–30%. Three studies have evaluated the effect of becoming obese on pulmonary function in adults without asthma, all of which confirm that reductions in both FEV₁ and FVC occur with increases in BMI over time^{33–35}. There is no other study of individuals without asthma followed from school age to young adulthood, as with the CAMP cohort.

The disparity between effects on pulmonary function as obesity develops in individuals without asthma, who develop a restrictive ventilatory defect, and those with asthma, who develop a worsening of their obstructive ventilatory defect, suggests different biologic mechanisms. Since FEV₁/FVC is normal in obese individuals without asthma, the source of the increased airway resistance in obesity appears to lie in the lung tissue³². The worsening in obstruction observed in patients with asthma is likely to be mediated by inflammatory mediators on airways.³⁶³⁷³⁸³⁹. Unfortunately, there are no data on inflammatory markers in the CAMP cohort and we are thus unable to determine their role in our finding of the development of abnormalities in lung function as children became obese.

In addition to the lack of measurement of inflammatory markers, our study has other limitations as well. Obesity was not a primary endpoint in the original study design. However, the prolonged follow-up of this cohort, along with the standard measurement of height and weight over all the visits, allowed us to adequately calculate BMI during visits during young adulthood. Forno et al. demonstrated that in 6–14 year old children in Puerto Rico, waist circumference was significantly associated with a decrement in FEV₁/FVC⁴⁰, however, BMI was the only measure of obesity and adiposity available throughout the longitudinal follow-up in CAMP. Similarly, Al-Alwan et al.⁴¹ found that respiratory system resistance and frequency dependence of resistance as assessed by impulse oscillometry

better discriminated effects of weight reduction surgery in obese adults with asthma than in controls than spirometry, but impulse oscillometry measures were not obtained in CAMP.

Another constraint is that while both groups of participants in our study were non-obese in childhood on trial entry based on the standard definition of childhood obesity (BMI percentile <95th percentile), those who became obese in young adulthood started out with a significantly higher BMI percentile than the non-obese group. This suggests that, while all children had a BMI considered non-obese at baseline, the group that became obese may have already been on a different trajectory compared with the non-obese group.

Finally, while measures of impairment and risk were collected systematically at each visit, the intervals between follow-up visits in young adulthood were 12 months. It is possible that recall of symptoms and prednisone use may have become less precise with time.

Conclusions

In this cohort of children with asthma who were non-obese at baseline (age 5–12 years), those who were obese during visits when 20 years or older had more obstructive pulmonary function compared to those who remained non-obese. The pulmonary function changes in the obese group during young adulthood were not associated with increased symptoms or exacerbation risk. However, the association between obesity and overall worsening of asthma control in adults suggests that obesity in young adults observed in CAMP may progress to having worsening asthma due to their obesity later in life. As those in the CAMP cohort who were obese in early adulthood differentiated themselves at school age with a higher BMI percentile, school age children with mild-moderate asthma who have a BMI indicative of an overweight status may represent an at risk group requiring careful monitoring of weight gain and early education about diet and exercise.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BMI	Body mass index
CAMP	Childhood Asthma Management Program
FEV₁	Forced expiratory volume in the first second

FVC	Forced vital capacity
PC20-FEV1	airway hyper responsiveness was defined as the concentration of methacholine that caused a decrease of 20% from baseline FEV ₁
ATS-DLD-78-C	American Thoracic Society's Division of Lung Diseases questionnaire for children
Pediatric definition of obesity	BMI 95th percentile
Adult definition of obesity	BMI 30 kg/m ²

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Highlight Box

1. What is already known about this topic? The finding that obesity is associated with airway obstruction in children has been examined only in cross sectional studies. (word count 19)
2. What does this article add to our knowledge? This longitudinal study demonstrates that children with mild to moderate asthma who became obese in young adulthood had worse obstructive pulmonary function compared to those who remained non-obese. (word count 28)
3. How does this study impact current management guidelines? Development of obesity by young adulthood in subjects with childhood asthma was associated with worsening obstructive pulmonary function, emphasizing the importance of monitoring weight in children with asthma as they grow into adulthood. (word count 33)

Table 1

Distribution of baseline characteristics of CAMP children by obesity* status in young adulthood

	Non-obese group: Not obese at baseline, not obese at any visit where age 20 years (N = 579)	Became-obese group: Not obese at baseline, obese during at least one visit where age 20 years (N = 192)	P†
<i>Demographics</i>			
Race/ethnicity, N (%)			0.005
White	427 (73.8)	121 (63.0)	
Black	66 (11.4)	30 (15.6)	
Hispanic	38 (6.6)	26 (13.5)	
Other	48 (8.3)	15 (7.8)	
Gender, N (%)			0.97
Male	340 (58.7)	113 (58.9)	
Female	239 (41.3)	79 (41.2)	
Age at randomization	8.7 ± 2.2	9.2 ± 1.9	0.008
Family income 50k at baseline, N (%)	257 (46.1)	71 (38.8)	0.08
BMI percentile at baseline	51.3 ± 26.6	76.6 ± 17.0	<0.0001
<i>PF measures</i>			
PreBD FEV1 % predicted at baseline	92.6 ± 13.8	92.7 ± 14.6	0.94
PreBD FVC % predicted at baseline	102.3 ± 12.2	102.3 ± 13.0	0.96
PreBD FEV1/FVC at baseline	80.1 ± 8.3	79.5 ± 8.5	0.46
PreBD FEV1/FVC % predicted at baseline	90.7 ± 9.1	90.5 ± 9.7	0.76
<i>Airway responsiveness</i>			
Log FEV1 PC20 at baseline, mg/mL	0.03 ± 1.1	0.20 ± 1.1	0.08
<i>Atopy</i>			
Log eosinophil count at baseline	5.8 ± 1.2	5.8 ± 1.1	0.50
Log IgE at baseline	6.1 ± 1.5	6.1 ± 1.5	0.70
Any positive skin test at baseline, N (%)	512 (88.4)	175 (91.2)	0.30
<i>Exposures</i>			
Treatment group, N (%)			0.21
Budesonide	176 (30.4)	48 (25.0)	
Nedocromil	168 (29.0)	67 (34.9)	
Placebo	235 (40.6)	77 (40.1)	
Ever been water damage to home, N (%)	297 (34.0)	70 (36.5)	0.54
Mold or mildew in home in the past year, N (%)	3150 (54.5)	112 (58.6)	0.32
Furry or feathered pets in home, yes vs. no, N (%)	372 (64.3)	128 (66.7)	0.54
<i>Asthma characteristics</i>			
Asthma severity at baseline, N (%)			0.25
Mild	278 (48.0)	83 (43.2)	
Moderate	301 (52.0)	109 (56.8)	
ICS use in 6 months prior to enrollment, yes vs. no, N (%)	223 (38.8)	72 (37.7)	0.79

* Obesity defined as BMI ≥ 30 mg/m²

[†] Chi square test for categorical variables and student T test for measured variables

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Table 2

Unadjusted and adjusted linear regression models of pulmonary function, pre- and post-bronchodilator, and measures of clinical status by obesity status* at each visit where participant 20 years of age

Outcome measures	Unadjusted [†]			Adjusted [‡]		
	N	Difference in outcome measure, obese vs. non-obese, b [§]	P	N	Difference in outcome measure, obese vs. non-obese, b [§]	P
Pre-bronchodilator Spirometry measures at each visit						
PreBD FEV1 % predicted	4885	-1.67	0.08	4631	-3.06	0.001
PreBD FVC % predicted	4885	-0.02	0.98	4631	-1.14	0.15
PreBD FEV1/FVC% predicted	4885	-1.82	0.005	4631	-2.24	0.0009
Post-bronchodilator spirometry measures at each visit						
PostBD FEV1 % predicted¶	4640	-2.29	0.01	4419	-3.54	<0.0001
PostBD FVC % predicted¶	3942	0.04	0.96	3864	-0.95	0.20
PostBD FEV1/FVC % predicted¶	3942	-2.21	0.0001	3864	-2.73	<0.0001
Measures of clinical status at each visit						
Wheeze without cold, y vs. n, (Odds Ratio) §	4969	1.12	0.42	4858	1.05	0.72
Shortness of breath while playing, y vs. n, (Odds Ratio) §	4969	1.05	0.73	4858	0.98	0.89
Prednisone course since last visit, y vs. n, (Odds Ratio)§	4969	1.46	0.07	4858	1.36	0.15

* Obesity defined as BMI ≥ 30 mg/m². Only patients who were non-obese at baseline were included in the analyses

[†] Models adjusted for spirometry at baseline (in models where spirometry is the dependent variable) only.

[‡] Models adjusted for race/ethnicity, gender, age at baseline, log IgE at baseline, BMI percentile at baseline, ICS use since previous visit, and spirometry at baseline (in models where spirometry is the outcome measure). With the exception of when also the dependent variable, models are also adjusted for wheeze without a cold at each visit.

[§] beta coefficient measures the difference in each outcome measure among groups obese vs. non-obese at each visit. Separate unadjusted and adjusted models were created for each outcome measure. Generalized Estimating Equations (GEE) was used to account for repeated measures.

Table 3

Adjusted[‡] means for pre- and post-bronchodilator spirometry measures by obesity status at each visit where participant ≥ 20 years of age

	Obese		Not Obese	
	Mean	CI	Mean	CI
PreBD FEV1 %predicted	89.0	(87.2, 90.8)	92.1	(91.3, 92.8)
PreBD FVC %predicted	101.0	(99.5, 102.6)	102.2	(101.5, 102.9)
PreBD FEV1/FVC %predicted	88.3	(87.1, 89.5)	90.5	(89.9, 91.2)
PostBD FEV1 %predicted	93.2	(91.7, 94.8)	96.8	(96.1, 97.5)
PostBD FVC %predicted	101.6	(100.3, 103.0)	102.6	(101.9, 103.2)
PostBD FEV1/FVC %predicted	92.8	(91.7, 93.8)	95.5	(94.9, 96.1)

* Obesity defined as BMI ≥ 30 kg/m². Only patients who were non-obese at baseline were included in the analyses

[‡] Models adjusted for race/ethnicity, gender, age at baseline, log IgE at baseline, BMI percentile at baseline, ICS use and wheeze without a cold since previous visit at each visit, and spirometry at baseline.

Table 4

Unadjusted and adjusted linear regression models of pulmonary function, measures, pre= and post-bronchodilator, and measures of clinical status by BMI at each visit where participant 20 years of age

Outcome measures	Unadjusted [†]			Adjusted [‡]		
	N	Change in outcome measure per change in BMI, b	P	N	Change in outcome measure per change in BMI, b	P
Pre-bronchodilator Spirometry measures at each visit						
PreBD FEV1 % predicted	4885	-0.09	0.28	4631	-0.29	0.0009
PreBD FVC % predicted	4885	0.12	0.13	4631	-0.01	0.94
PreBD FEV1/FVC % predicted	4885	-0.21	0.0005	4631	-0.31	<0.0001
Post-bronchodilator spirometry measures at each visit						
PostBD FEV1 % predicted ¶	4640	-0.13	0.08	4419	-0.32	<0.0001
PostBD FVC % predicted ¶	3942	0.11	0.10	3864	0.02	0.80
PostBD FEV1/FVC¶	3942	-0.23	<0.0001	3864	-0.35	<0.0001
Measures of clinical status at each visit						
Wheeze without cold, y vs. n, (Odds Ratio) §	4969	1.01	0.56	4858	0.99	0.65
Shortness of breath while playing, y vs. n, (Odds Ratio) §	4969	1.00	0.91	4858	0.99	0.60
Prednisone course since last visit, y vs. n, (Odds Ratio)§	4969	1.02	0.18	4858	1.02	0.39

[†] Models adjusted for spirometry at baseline (in models where spirometry is the dependent variable) only. Generalized Estimating Equations (GEE) was used to account for repeated measures.

[‡] Models adjusted for race/ethnicity, gender, age at baseline, log IgE at baseline, BMI percentile at baseline, ICS use since previous visit, and spirometry at baseline (in models where spirometry is the outcome measure). With the exception of when also the dependent variable, models are also adjusted for wheeze without a cold at each visit.