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Obesity and asthma, an association modified by age of asthma onset

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Abstract

Background—Studies of asthma phenotypes have identified obesity as a component of a group characterized by a high proportion of adult-onset asthmatics. However, whether age of asthma onset modifies the association between obesity and asthma is unknown.

Methods—From the Severe Asthma Project (SARP), we defined age of asthma onset as early (before 12 years of age) and late-onset (12 and higher). Comparisons of body mass index (BMI) categories were done within age of onset groups and obesity was also compared across these groups. Multivariable logistic regression analysis was done to evaluate the association between BMI categories with healthcare utilization and respiratory symptoms and multivariable linear regression for the association between duration of asthma and weight gain (BMI change/yr). An interaction between obesity and age of asthma onset was included in the multivariable analyses.

Results—The study population consisted on 1,049 subjects of which the median age for asthma onset was 10 years (IQR 4 – 25); 48% were late-onset (≥ 12) and 52% were early-onset (<12). Compared to late-onset obese asthmatics, early-onset obese asthmatics had more airway obstruction, bronchial hyperresponsiveness, and higher OR of ever having 3 or more oral steroid tapers preceding/year or ICU admissions for asthma/preceding year (Interactions between obesity and age of asthma onset were respectively $p=0.055$ and $p=0.02$). In early-onset, but not in late-onset asthmatics, there was a significant association between increasing BMI and duration of asthma, after adjusting for confounders. The interaction between asthma duration and age of asthma onset was $p < 0.01$.

Conclusion—Asthmatics are differentially affected by obesity, based on whether they developed asthma early (<12 years) or later in life. These results highlight the need to understand obesity as a comorbidity that affects specific clinical phenotypes and not all asthma subjects alike.

Keywords

Severe; asthma; obesity; SARP

Introduction

Compared to lean and overweight subjects with asthma, obese asthmatics have more severe and frequent respiratory symptoms, greater exacerbation rates and reduced asthma-related quality of life¹. Several mechanisms have been postulated as potential explanations to understand how obesity affects asthma, including increased airway resistance, abnormal respiratory mechanics, increased bronchial hyperresponsiveness, and reduced inhaled corticosteroid effectiveness^{2–6}. However, in clinical studies obesity has not been consistently associated with increased airway inflammation, and clinical impairment^{7–10}. This lack of consistency may be partly determined by our inability to determine in which asthmatics obesity is a comorbidity that affects the underlying pathophysiology of asthma or the response to therapy vs. being primarily a driver of increased respiratory symptom burden. Evidence that obesity does not equally affect all asthmatics is supported by cluster analysis studies which have identified obesity as part of a clinical asthma phenotype characterized by higher proportion of females and late-onset disease^{11,12}. Having late-onset asthma, typically during early adolescence or adulthood, is associated with a different clinical phenotype. While late-onset asthmatics are characterized by having less atopy and a higher degree of airway eosinophilic inflammation, early early-onset asthmatics have more allergic symptoms, atopy, higher IgE levels and proportionately less eosinophilic inflammation^{13,14}. Based on the fact that obesity has been predominantly associated with the late-asthma onset phenotype, we hypothesized that the influence of obesity on asthma control and severity characteristics is modified by the age of asthma onset (early-onset vs. late-onset). We also explored whether age of asthma onset would differentially affect the degree of body mass index (BMI) change over time and the risk of being obese. A cross-

sectional analysis using data from the NIH Severe Asthma Research Program (SARP) was used to address these questions.

Methods

Study Population

The study population consisted of participants ages 18 or older from the multi-center SARP study that met criteria for asthma, which included either a 12% increase in FEV₁ after short acting bronchodilator or a 20% drop in FEV₁ after inhalation of methacholine (PC₂₀ 25 mg/ml). The SARP study has been previously described in detail¹⁵. Briefly, the study population consisted on subjects recruited at each of the SARP participating academic centers through the use of local advertisement, which met eligibility criteria, including: being a current nonsmoker with asthma and having less than 5 pack-years of tobacco use. Study participants were classified as having mild, moderate or severe asthma. According to the American Thoracic Society (ATS) definition, severe asthma was defined as: at least 1 major criteria: a) Use of high-dose inhaled steroids for > 50% of the preceding year, b) continuous or near-continuous oral steroids; and at least 2 minor criteria: a) daily controller medication in addition to inhaled steroids, b) beta agonist required daily or near-daily, c) persistent airway obstruction, d) one or more urgent care visits for asthma per year, e) 3 or more oral corticosteroid bursts/year, f) clinical deterioration with reduction in oral steroid dose, and g) near-fatal asthma event in the past. Non-severe asthmatics included those with moderate (pre bronchodilator FEV₁ < 80% with or without use of inhaled corticosteroids (CS)) or mild (FEV₁ ≥ 80% with or without use of inhaled CS) asthma¹⁶. For purposes of this study, mild and moderate asthmatics were analyzed together as “not severe” asthma. Age of onset was dichotomized into early childhood (< 12 years) and adolescent / late-onset (≥ 12 years), based on data showing that this age dichotomy differentiates severe asthma into distinct inflammatory phenotypes¹⁴.

Clinical Data

After signing informed consent, study participants provided demographic information, smoking history, past medical history and frequency of respiratory symptoms in the 3 months preceding enrollment, including cough, sputum production, chest tightness, nighttime asthma symptoms, wheezing, and shortness of breath. Subjects also completed the Juniper Asthma Quality of Life Questionnaire (AQLQ)¹⁷.

Allergy Skin Test

All participants underwent allergy skin testing for tree mix, grass mix, ragweed, weed mix, dogs, cats, molds, dust mites, and cockroach. To control for validity, diluting fluid and histamine were respectively used as negative and positive controls. Presence of atopy was defined as having at least one skin test reaction of ≥3 mm and greater than the saline control.

Lung Function testing

Spirometry was done following ATS guidelines. Post bronchodilator FEV₁ was recorded as the maximum bronchodilator change between 4 and 8 puffs of albuterol¹⁸. Patients with a baseline FEV₁ > 50% and FEV₁ ≥ 1.5L underwent methacholine challenge, following a 7-dose algorithm of incremental doses from 0.078mg/ml to maximum of 25 mg/ml. A provocation concentration (PC₂₀) of <25 mg/ml was considered positive. This high value was chosen because of the high and prolonged steroid doses in the population. Because of FEV₁ criteria, methacholine were only done a subset of the subjects.

Inflammatory biomarkers

Total serum IgE, complete blood count with cell count differential was done using standard clinical laboratory procedures. In subjects with an FEV₁% predicted >55%, sputum induction and processing were performed using a standardized protocol based on the Fahy method using 3% saline for induction¹⁹. Sputum eosinophils were counted by a single reader and presented as percent of total white blood cells in sputum. Similar to methacholine, sputum was only obtained on a subset of subjects. On line exhaled nitric oxide was performed following the ATS recommendations in a subset of study subjects²⁰.

Statistical Analysis

Given that the majority of continuous variables in Table 1 did not achieve normality using the Kolmogorov-Smirnov test for both late and early onset asthma groups, comparisons of continuous variables within and between groups were done using a more conservative non-parametric analysis with Kruskal-Wallis for the BMI categories or Wilcoxon's rank sum for comparison of obese categories across age of asthma onset groups. Chi square or Fisher's exact test were used for comparison of proportions. Some comparisons across age of onset groups were done on smaller subsets of patients in whom the comparison test was not performed in the entire group. A Bonferroni correction of $\alpha=0.05/\kappa$ (κ =number of BMI categories) was used to reduce the likelihood of false positives due to multiple group comparisons. The Bonferroni-corrected p value is set at $p < 0.016$.

Multivariable and univariable logistic regression analysis combined severe and non-severe asthmatics to model the association between BMI categories (main exposure) and asthma morbidity measures in the preceding 12 months from SARP enrollment. Asthmatics of different severity were combined given that the categories of asthma severity were included part of the outcomes evaluated by the model. The dichotomous outcomes for the logistic regression analyses included the following events in the preceding year of SARP enrollment: having three or more steroid bursts, visited the emergency department for asthma, spent at least one night in a hospital for breathing reasons, and any intensive care unit admissions for asthma; also, having ever been mechanically ventilated for asthma-related reasons and been diagnosed with pneumonia. Modeling was done via backward elimination with retention of variables in the model based on a significance level ≤ 0.1 or a $\pm 10\%$ change in the model estimate. These models were adjusted for asthma duration in years, atopy (yes/no) and race (Caucasian or African American or other); use of asthma controller medications (current use vs. no use, including inhaled steroids, long acting beta agonists or Leukotriene blockers); age and gender were not significant and thus were not included in the final model. Multivariable logistic analysis was also used to model having continuous respiratory symptoms (in the preceding 3 months prior to SARP enrollment), which was defined as having any of the following: cough, sputum production, chest tightness, wheeze, dyspnea, and nocturnal asthma symptoms, two or more times per week. Other outcomes included having an asthma quality of life questionnaire below the population's median level (4.6) and being labeled as having severe asthma (yes/no). These models were adjusted for atopy (yes/no), asthma duration (years), gender, and race (Caucasian, or African American, or other). Results are presented as univariable and adjusted estimates. All multivariable logistic models included an interaction term between obesity and age of asthma onset.

To determine whether age of asthma onset is a risk factor for weight gain, the linear association between years of having asthma (main exposure) and BMI as a continuous variable (model outcome) was modeled adjusting for gender, race, and asthma severity. The interaction between age of asthma onset and BMI was evaluated to determine whether a

statistically significant differential weight pattern exists between early or late asthma phenotypes.

Results

The study population consisted on 1,049 adult subjects with asthma of which 63% were female, 65% were Caucasian, 27% were African American, and 8% other. The median age for asthma onset was 10 years (IQR 4 – 24), 48% were late-onset (25 years, range: 12 – 69) and 52% were early-onset (4 years, range: 0 – 11). The median BMI was 28 (IQR 23 – 34), 42% were obese, 27% overweight and 31% lean. Within the late onset group 48% were obese (BMI 35 IQR 32.7 – 40.7), 25% overweight (BMI 27 IQR 26 – 28.5); 26% lean (BMI 22.8 IQR 21.2 – 23.8). BMI was correlated with age among late onset (Spearman's rho 0.12, $p < 0.01$) and to a greater extent within early onset asthmatics (Spearman's rho 0.23, $p < 0.01$). Age was also associated with asthma duration in the late onset (Spearman's rho 0.4, $p < 0.01$) and early onset (Spearman's rho 0.9, $p < 0.01$) asthmatic groups. The proportion of severe and non-severe asthmatics was respectively 42% and 58% for the entire study population. Among late onset asthmatics these proportions were respectively 47% and 53%, and among the early onset asthmatics 37% and 63%.

Demographic, functional and phenotypical comparisons between obese and non-obese asthmatics within each age of asthma onset categories

Table 1 shows the distribution of demographic, lung function and biomarkers of allergic inflammation by age of asthma onset. Among early-onset asthmatics, the obese and overweight were older, had a larger proportion of African American subjects, and had asthma for a longer period of time than lean asthmatics. Compared to leaner counterparts, a larger proportion of obese early-onset asthmatics were on controller medications. There was a trend for lower FEV₁ and FVC % predicted values with increasing BMI categories (p trend for both $p=0.001$) and a trend for greater airway obstruction (determined by FEV₁/FVC) and maximal FEV₁ reversal after short acting bronchodilators (p trend < 0.001 and $p=0.002$, respectively). There was a marginal inverse trend (trend $p=0.06$) between exhaled NO and BMI categories (based on a subset of 411 early-onset asthmatics).

Among the late-onset category, obese and overweight asthmatics were older and their age of asthma onset was at an older age when compared to leaner asthmatics. The race distribution differed across the late-onset BMI categories, with a greater proportion of African American being in the obese category. Obese late-onset asthmatics were also more likely to be classified as having severe asthma and required more asthma control medications. Among the late-onset asthmatics there was a trend for lower FEV₁ and FVC % predicted values (p trend for both $p=0.001$) with increasing BMI categories.

Demographic, functional and phenotypical comparisons between age of asthma onset categories

Early-onset obese asthmatics were younger and had a lower proportion of females than the obese late-onset. Also, early-onset obese asthmatics had greater airway obstruction and a marginally higher maximal FEV₁ reversal when compared to late-onset obese asthmatics. Among a subset of SARP participants with methacholine testing (early-onset $n=359$, late-onset $n=306$) obese early-onset asthmatics had significantly greater bronchial hyperresponsiveness when compared to obese late-onset obese asthmatics ($p=0.0009$). Non-obese early-onset asthmatics also had greater bronchial responsiveness than late-onset non-obese, but to a lesser extent ($p=0.049$). Also, obese early-onset asthmatics had higher IgE levels when compared to the obese late-onset (based on a subset of 406 early-onset and 361 late-onset asthmatics); IgE levels were not significantly different between non-obese early

and late-onset asthmatics. The proportion of atopic asthmatics was higher in obese and non-obese early-onset asthmatics, compared to late-onset obese and non-obese asthmatics.

Respiratory symptoms, quality of life and asthma severity

Obese early-onset asthmatics were more likely to have continuous cough, sputum production, chest tightness, wheeze, dyspnea, asthma nocturnal symptoms, have lower asthma-related quality of life, and severe asthma when compared to the leaner early-onset categories. Obese late-onset asthmatics were also more likely than the leaner late-onset BMI categories to have increased continuous respiratory symptoms, reduced quality of life, and to be labeled as having severe asthma. Unlike the early asthma onset category, sputum production and chest tightness were not associated with obese or overweight late-onset asthma. The magnitude of associations between BMI categories with respiratory symptoms, quality of life and asthma severity was similar across age of asthma onset categories (no significant interactions) (See Table 2 and Table E2 in the supplement).

Asthma morbidity

Obese early asthmatics were more likely than non-obese to have had asthma exacerbations requiring oral steroids, use healthcare resources, including ER visits, hospitalizations, ICU admissions, and mechanical ventilation (See Table 3 and Table E3 in the supplement). In contrast, obese late-onset asthmatics were only more likely to have been admitted to the ED or the ICU when compared to non-obese late-onset asthmatics. Between categories of age of asthma onset, early-onset obese asthmatics had marginally greater odds for requiring 3 or more steroid tapers in the preceding year (interaction $p=0.055$) and being admitted to the ICU in the preceding year for asthma-related problems (interaction $p=0.02$).

Association between BMI and duration of asthma

The association between BMI and asthma duration was modeled adjusted for gender, race, and asthma severity while testing for an interaction with the age of asthma onset group. The rate of BMI increase for every year of having asthma among the early-onset group was $\beta=0.20$ 95% C.I. 0.07 – 0.33; ($p=0.002$) in comparison to the late-onset group, which was $\beta=-0.05$ 95% C.I. -0.17, .33; $p=0.4$ (The interaction between asthma duration and age of onset on BMI change was significant at $p < 0.008$) (See Figure 1).

Discussion

Given its high prevalence in the general population, obesity is one of the most frequent co-morbidities among subjects with asthma. Yet remarkably, the association between obesity and asthma severity has been inconsistent. This may be explained by a combination of factors, which include the fact that not every asthmatic is equally affected by increases in BMI and by the fact that age of asthma onset may lead to differential weight gain patterns. In other words, clinical or epidemiological studies have likely involved heterogeneous groups of asthmatic phenotypes, which have different degrees of susceptibility to being overweight or for being overweight. The results from this study support this assertion by showing that the association between being overweight or obese as a co-morbidity for asthma varies depending on whether asthma was acquired early in childhood (<12 yrs of age) or later in life (≥ 12 yrs of age). While the proportion of severe asthmatics, use of oral steroids and controller medications increase in relation to BMI categories in both groups, there are several important differences between them. Early-onset obese asthmatics were more likely to have increased airway obstruction (as determined by FEV₁/FVC), greater bronchial hyperresponsiveness and FEV₁ reversal after bronchodilators. Also, obese early-onset asthmatics had a larger IgE levels. These differences across age of asthma onset

groups were either not significant or less significant (i.e. bronchial hyperresponsiveness) when restricting the analysis to non-obese asthmatics.

In both groups being overweight or obese was associated with greater odds for several co-morbid outcomes and respiratory symptoms when compared to lean asthmatics; However, early-onset asthmatics had a marginal increase in the odds of having a high number of steroid bursts/year and were significantly more likely to be admitted to the ICU for asthma-related problems. Also, in contrast to late-onset obese asthmatics, early-onset obese asthmatics showed significantly increased odds for continuous chest tightness and sputum production. Interestingly, early-onset asthmatics had a steeper BMI increase for every year of having asthma, after adjusting for asthma severity, atopy, age and race.

Early and late-onset asthma are recognized as distinct asthma phenotypes with unique clinical and genetic features²¹. Early-onset asthmatics (before age 12) have a higher likelihood of allergic sensitization and reactions, history of eczema and tend to have higher IgE levels; in contrast, late-onset asthmatics have less atopy but greater airway eosinophilic inflammation²². Early-onset asthma has also been associated with single nucleotide polymorphisms (SNP) that bear no association with a later-onset phenotype²³. A sequence variant near the ORMLD3, a gene on chromosome 17q21 previously associated with childhood asthma, was confined to early-onset asthma cases only, an association replicated in 6 European and 1 Asian cohort.

Based on the fact that the early and late-onset asthma appear to be different phenotypes, it is reasonable to hypothesize that they are differentially impacted by increases in BMI. Although the longitudinal or cumulative effects of obesity on asthma are not known, in early-onset asthmatics obesity has been shown to be an independent risk factor for developing unremitting asthma beyond puberty²⁴. This suggests that there is an early-onset asthma phenotype in which obesity plays a role in developing persistent asthma. In late-onset asthma, especially during adulthood, there are no studies to date which have evaluated the longitudinal effect of obesity on asthma outcomes or biomarkers of disease activity, as the overwhelming majority of information is derived from cross sectional studies. However, recent studies suggest that obesity may be an important factor among asthmatics with specific phenotypical characteristics. Cluster analysis was used to identify specific asthma clusters in SARP participants based on demographic, clinical and lung function variables. Of the clusters identified, the largest proportion of obese asthmatics was observed in a cluster characterized by a higher female predominance, very late-onset asthma and less atopy. Similar to the SARP cluster study Haldar et al, identified obesity as a component of a cluster characterized by a larger proportion of females with less atopy and later onset asthma¹². Although our study did not find a significant gender interaction between obesity, age of asthma onset and gender, the majority of late-onset obese asthmatics were also female.

In evaluating whether age of asthma onset modifies the pattern of BMI increase, a cross sectional analysis stratified by age of asthma onset was done to evaluate the slope of BMI change in relation to the years of having asthma. These models were adjusted for gender, race, atopy and asthma severity categories. Age was not included in the model due to its high correlation with asthma duration in the early onset ($r^2=0.9$, $p < 0.01$). Early-onset asthmatics exhibited a steeper BMI increase for every year after being diagnosed with asthma even after adjusting for asthma severity (change in BMI for every year of having asthma with adjustment for asthma severity $\beta=0.2$ [95% 0.07 – 0.33] and without severity adjustment $\beta=0.3$ [95% 0.2 – 0.45]). In contrast, late-onset asthmatics did not show a significant linear change in BMI with duration of asthma, even when restricting analysis to those with severe asthma (data not shown). These results may imply that in early onset asthma, the association between obesity with increased asthma morbidity is the result of

more severe asthmatics gaining weight and becoming obese; whereas in late-onset asthma, the association between obesity and increased asthma severity is more likely to be cause (obesity) and effect (severity).

Interestingly, there were notable differences in the associations between lung function and biomarkers of inflammation with increasing BMI across age of onset groups. Increasing BMI categories in the early-onset group were associated with more airway obstruction, a trend for lower exhaled NO, but higher IgE levels, relationships not seen in the late onset group.

There are several limitations to consider when interpreting these results. There is likely some degree of recall bias in ascertaining the age of asthma onset; however, this bias is likely not related to BMI categories. However, the strength of the association of duration with BMI in the early onset group (and the lack of any relationship in late onset disease) argues that even for early onset disease, there is reasonably good recall. Also, given that this is a cross sectional study, it is impossible to fully ascertain the relationship between BMI and asthma at the time of asthma diagnosis. The SARP study does not include data on physical activity or exercise habits; therefore it is not possible to determine to what extent differences in weight gain and obesity risk across age of onset groups are driven by physical activity patterns. Although being obese may lead to asthma diagnostic bias²⁵, this is very unlikely to occur within the SARP study, given that all subjects with asthma are rigorously diagnosed using a standardized algorithm.

Recent data suggest that in the US, there are approximately 5 million adults and over 2 million children with current asthma who are obese (<http://www.cdc.gov/asthma/asthmadata.htm>). Based on the results of this and other studies, adult asthmatics experience higher end health care utilization, which translates into an enormous economic burden. Future studies to evaluate mechanisms by which obesity affects asthma should consider stratifying by age of asthma onset, as the relationship appears to be very different. Understanding the implications and mechanisms of obesity as it relates to asthma will allow targeted therapeutic interventions.

Clinical implication STATEMENT

These results suggest that in early onset-asthma, obesity and increased asthma severity results from severe asthmatics becoming obese; whereas in late-onset asthma, obesity and increased asthma severity are potentially more likely to be causatively associated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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List of abbreviations

AQLQ	Asthma quality of life questionnaire
BMI	Body mass index
CS	Corticosteroids
ED	Emergency department

FEV1	Forced exhaled volume in one second
FVC	Forced vital capacity
ICU	Intensive care unit
NO	Nitric oxide
PC20	Percent change 20% in FEV1 after methacholine
SARP	Severe Asthma Research program

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Figure 1. Association between BMI and years of having asthma, by age of asthma onset

Foot note: Linear regression models adjusted for gender, race, and asthma severity

Early onset asthma linear slope: $\beta=0.20$ 95% C.I. 0.07 – 0.33; ($p=0.002$)

Late onset asthma slope: $\beta=-0.05$ 95% C.I. -0.17, .33; ($p=0.4$)

Interaction of BMI and asthma duration by age of onset asthma $p < 0.008$

Table 1

Characteristics of the study population by age of onset asthma and BMI categories

BMI categories	Late-onset asthma n=506				Early-onset asthma n=543				Between age onset Obesity comparison p*
	>30 N=245	> 25 < 30 N=125	≤ 25 N=134	p	>30 N=201	> 25 < 30 N=153	≤ 25 N=189	p	
N=1047 (%)	245 (48)	125 (25)	134 (27)		201 (38)	153 (28)	189 (34)		
Demographic and clinical characteristics									
Body Mass Index	35.5 (33–41)	27 (26–28)	23 (21–24)		36 (33–40)	27 (26–28)	22 (20–23)		
Age (years) Median (range)	45 (20–79)	43 (19–74)	39 (18–78)	0.01	35 (18–75)	33 (18–66)	26 (18–69)	<0.01	<0.01
Gender: Female (%)	74	65	69	0.1	65	49	64	<0.01	0.03
Age at asthma onset (years)	27 (15–37)	26 (18–35)	22 (19–31)	<0.01	4 (1–7)	4 (1–7)	5 (2–7)	0.1	
Median asthma duration (years IQR)	14 (6–24)	11 (6–21)	12 (6–23)	0.40	31 (22–42)	30 (19–39)	22 (17–30)	<0.01	<0.01
Race: Caucasian (%)	61	70	72	<0.01	50	68	75	<0.01	0.01
African American (%)	34	24	13		42	24	17		
Other (%)	5	6	15		8	8	8		
Ex-smoker (%)	20	23	26	0.20	21	17	14	0.70	0.70
Median amount smoked (PPY IQR)	4 (1–5)	4 (1–8)	3 (0–10)	0.20	2 (1–5)	1 (0–4)	2 (1–4)	0.40	0.60
Severity (%) : Mild	23	36	44		25	44	50		
Moderate	23	23	18	<0.01	24	22	25	<0.01	0.70
Severe	54	41	38		51	34	25		
Exercise provokes asthma symptoms (%)	82	83	76	0.30	87	86	88	0.80	0.10
Medications									
Any ICS Steroid Use (%)	75	69	69	0.40	69	59	65	0.40	0.20
High dose ICS (%)	54	40	37	<0.01	50	34	26	<0.01	0.10
OCS Steroid Use (%)	20	12	8	<0.01	17	9	7	<0.01	0.10
LABA Use (%)	72	60	62	0.04	69	61	55	0.02	0.40
Leukotriene blockers (%)	44	30	30	<0.01	31	26	21	0.07	0.02
Any Anti IgE Use (%)	10	1	2.2	<0.01	16	4	5	.3	0.60
Lung Function Test									

BMI categories	Late-onset asthma n=506				Early-onset asthma n=543				Between age onset Obesity comparison p [*]
	>30 N=245	>25 <30 N=125	≤25 N=134	p	>30 N=201	>25 <30 N=153	≤25 N=189	p	
FEV1 L median (IQR)	2.1 (1.7 – 2.7)	2.5 (1.7 – 2.9)	2.5 (1.7 – 3.3)	<0.01	2.2 (1.6 – 2.7)	2.9 (2.1 – 3.7)	2.8 (2.3 – 3.4)	<0.01	0.80
FEV1 % Pred median (IQR)	75 (57–86)	76 (59–89)	81 (58–95)	0.04	70 (54–83)	82 (66–94)	82 (69–97)	<0.01	.09
FVC L median (IQR)	2.9 (3.4 – 3.6)	3.4 (2.7 – 4.1)	3.6 (2.8 – 4.2)	<0.01	3.1 (2.5 – 3.8)	4 (3.1 – 4.7)	3.8 (3.2 – 4.6)	<0.01	0.10
Base FVC % Pred (Median IQR)	79 (69 – 94)	85 (75 – 97)	90 (78 – 101)	<0.01	83 (71–94)	94 (82–105)	94 (71–94)	<0.01	0.20
Base FEV1/FVC (Median IQR)	.73 (.63–.8)	.71 (.60–.80)	.72 (.60–.80)	0.10	.69 (.59–.76)	.72 (.62–.78)	.73 (.64–.82)	<0.01	<0.01
Max FEV1 reversal (%) (Median IQR)	12 (5–22)	11 (5–21)	10 (4–19)	0.50	14 (6–26)	12 (7–19)	10 (6 – 18)	<0.01	0.06
Pc20 (mg/ml) [*] (Median IQR)	1.5 (4–5)	1.4 (4 – 3)	1.6 (5–6)	0.70	0.7 (3–2.2)	1 (2–4)	1 (3–3)	0.20	<0.01
Biomarkers for Allergy									
IgE IU/ml ^{**} (Median IQR)	165	194	284	0.10	540	255	348	0.80	<0.01
Exhaled NO (ppb) (Median IQR)	36	38	43	0.20	33	43	46	0.08	0.80
Atopic (%) [§]	72	82	79	0.07	86	93	92	0.09	<0.01
Percentage of EOS in Blood [‡] (Median IQR)	4 (2 – 6)	3 (1 – 5)	3 (1 – 6)	0.50	3 (2 – 5)	3 (2 – 5)	4 (2 – 6)	0.40	0.60
Percentage of EOS in Sputum [‡] (Median IQR)	1.5 (4–5)	1 (2 – 4)	3 (2–14)	0.20	1 (2 – 4)	.6 (1–4)	.8 (3–5)	0.20	0.60

Obesity comparison: Between age of onset group, limited to BMI > 30

^{*} Based on a subset of 665 asthmatics (359 early, and 306 late)

[§] Positive reaction to at least 1 skin allergen, sample limited to 468 early and 435 late-onset asthmatics

[‡] Based on a subset of 492 asthmatics (232 late, 260 early)

^{**} Based on a total of 406 early and 361 late-onset asthmatics

[‡] Based on a total of 819 asthmatics (438 early, and 381 late)

Except were stated continuous variables are shown in median and interquartile ranges (25 – 75th)

LABA: Long acting beta blockers
NO: nitric oxide
EOS: eosinophils
ICS: Inhaled corticosteroids
OCS: oral corticosteroids

Table 2

Examination of morbidity association by age of asthma onset with BMI categories

	Late-onset asthma OR (95% C.I.)		Early-onset asthma OR (95% C.I.)	
	Univariable N= 506	Multivariable N=435*	Univariable N=543	Multivariable N=468*
Cough				
Lean	1.0	1.0	1.0	1.0
Overweight	1.3 (0.7 – 2.2)	1.1 (0.6 – 2)	1.02 (0.6 – 1.8)	0.9 (0.5 – 1.8)
Obese	1.9 (1.6 – 4.2)	1.7 (1.01 – 2.9)	2.6 (1.6 – 4.2)	2.2 (1.3 – 3.9)
Sputum				
Lean	1.0	1.0	1.0	1.0
Overweight	0.7 (0.4 – 1.3)	0.6 (0.3 – 1.2)	1.2 (0.7 – 2.4)	1.2 (0.6 – 2.4)
Obese	1.3 (0.8 – 2)	1.1 (0.7 – 1.9)	2.8 (1.6 – 4.7)	2.5 (1.3 – 2.5)
Chest tightness				
lean	1.0	1.0	1.0	1.0
Overweight	0.9 (0.5 – 1.6)	0.8 (0.4 – 1.6)	1.0 (0.6 – 1.9)	0.9 (0.5 – 1.6)
Obese	1.6 (0.9 – 2.6)	1.4 (0.8 – 2.4)	1.4 (1.4 – 3.5)	1.8 (1.05 – 3)
Wheeze				
lean	1.0	1.0	1.0	1.0
Overweight	1.0 (0.5 – 1.9)	1.1 (0.6 – 2.5)	1.0	0.7 (0.4 – 1.4)
Obese	2.2 (1.3 – 3.6)	2.2 (1.3 – 3.4)	3 (1.9 – 5)	2.7 (1.6 – 4.7)
Dyspnea				
lean	1.0	1.0	1.0	1.0
Overweight	0.8 (0.5 – 1.3)	0.8 (0.4 – 1.3)	1.0 (0.6 – 1.7)	0.8 (0.4 – 1.4)
Obese	2.4 (1.5 – 3.7)	1.7 (1.02 – 3.3)	2.4 (1.5 – 3.7)	2 (1.2 – 3.3)
Nocturnal symptoms				
lean	1.0	1.0	1.0	1.0
Overweight	1.0 (0.5 – 1.9)	0.9 (0.5 – 1.9)	0.8 (0.4 – 1.6)	0.7 (0.4 – 1.3)
Obese	2 (1.2 – 3.3)	2.1 (1.1 – 3.6)	2.1 (1.4 – 3.4)	1.7 (1.02 – 3.3)
Low AQLQ				
lean	1.0	1.0	1.0	1.0
Overweight	1.9 (0.9 – 3.5)	2.3 (1.3 – 4.7)	0.9 (0.5 – 1.6)	0.8 (0.4 – 1.6)
Obese	2.8 (1.6 – 4.8)	2.8 (1.5 – 5.4)	2.9 (1.8 – 4.8)	2.4 (1.4 – 4.3)
Severe asthma				
Lean	1.0	1.0	1.0	1.0
Overweight	1.1 (0.6 – 1.8)	1.23 (0.7 – 2.2)	1.1 (0.7 – 1.8)	0.9 (0.5 – 1.6)
Obese	1.9 (1.2 – 2.9)	1.85 (1.1 – 3)	1.9 (1.2 – 2.9)	2.1 (1.3 – 3.5)

* Limited to asthmatics with documented atopy by skin testing

Adjusted for age, gender, race, atopy, and asthma duration.

Bolded estimates are significant at $p < 0.05$; This significance is for the comparison of either overweight or obese in reference to the lean category within age of asthma categories

Across age of asthma categories, comparisons were done using an obesity-age of onset interaction in the model. No significant interactions were observed.

Table 3

Association between age of asthma onset with asthma morbidity outcomes

	Late-onset asthma OR (95% C.I.) N=435*		Early-onset asthma OR (95% C.I.) N=468*	
	Univariable N= 506	Multivariable N=435*	Univariable N=543	Multivariable N=468*
3 or more steroid tapers / year				
Lean	1.0	1.0	1.0	1.0
Overweight	1.2 (0.7 – 2)	1.04 (0.6 – 1.5)	1.4 (0.8 – 2.4)	1.3 (0.7 – 2.5)
Obese	1.5 (0.9 – 2.4)	1.11 (0.6 – 1.9)	2.7 (1.6 – 4.4)	2.4 (1.3 – 4.2)
Visited ED preceding year				
Lean	1.0	1.0	1.0	1.0
Overweight	1.3 (0.8 – 2.4)	1.6 (0.9 – 3)	1.2 (0.7 – 2)	1.06 (0.6 – 1.9)
Obese	2.2 (1.3 – 3.5)	2.0 (1.1 – 3.4)	2.4 (1.5 – 3.9)	1.8 (1.5 – 2.3)
Spent the night in the hospital for breathing reasons in the preceding year				
lean	1.0	1.0	1.0	1.0
Overweight	1.6 (0.7 – 3.4)	1.9 (0.8 – 4)	2.4 (1.1 – 5.3)	1.8 (0.8 – 4)
Obese	2.6 (1.3 – 5)	2.2 (0.9 – 5)	4 (1.9 – 8.3)	3.3 (1.5 – 7)
Admitted to ICU for asthma reasons / preceding year				
lean	1.0	1.0	1.0	1.0
Overweight	2.2 (0.6 – 7)	2.2 (0.6 – 7)	3 (0.7 – 11)	2 (0.4 – 8)
Obese	2.3 (0.7 – 7)	1.3 (1.4 – 5)	6.5 (2 – 22)	6 (1.7 – 22)
Mechanical ventilation ever				
lean	1.0	1.0	1.0	1.0
Overweight	1.0 (0.4 – 2.6)	1.0 (0.4 – 2.6)	1.3 (0.6 – 2.8)	1.0 (0.4 – 2.3)
Obese	1.2 (0.6 – 2.6)	.99 (0.2 – 2.2)	2.6 (1.4 – 5)	2.08 (1.1 – 4.3)
Pneumonia diagnosis ever				
lean	1.0	1.0	1.0	1.0
Overweight	1.1 (0.6 – 1.9)	1.1 (0.6 – 1.9)	1.2 (0.8 – 2)	1.3 (0.8 – 2.2)
Obese	1.6 (1.03 – 2.5)	1.5 (0.9 – 2.4)	2.4 (1.6 – 3.4)	2.2 (1.4 – 3.7)

* Limited to asthmatics with documented atopy by skin testing

Adjusted for age, gender, race, atopy, and asthma duration.

Bolded results: p <0.05

Bolded estimates are significant at p < 0.05; This significance is for the comparison of either overweight or obese in reference to the lean category within age of asthma categories

Across age of asthma categories, comparisons were done using an obesity-age of onset interaction in the model.

Obesity and age of onset interactions

3 or more steroid tapers: p=0.055

Admitted to the ICU for asthma: $p=0.02$
Bolded estimates are significant at $p < 0.05$