

PEDIATRIC

Asthma Severity, Exacerbation Risk, and Controller Treatment Burden in Underweight and Obese Children

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Objective. The relationship between weight status and asthma characteristics in children remains inadequately defined. Very little has been published on the risk of exacerbation, physician perception of severity, and the level controller treatment prescribed to underweight and obese children with asthma in a real-world setting. **Methods.** We assessed the diagnostic severity, pulmonary function, exacerbation prevalence, and controller treatment level in 10,559 new asthma patients seen at one of four pediatric asthma subspecialty clinics among three BMI groups. Participants were analyzed by body mass index (BMI)-percentile based on Centers for Disease Control & Prevention classification. Multivariable logistic regression models were used to assess the associations between BMI-percentile cohort group and asthma outcomes. **Results.** Underweight asthmatics were rare (2.5%) relative to obese asthmatics but appeared to have the greatest impairment in forced vital capacity and had the greatest controller treatment burden. Obese asthmatic children made up 26.2% of our cohort and were more likely to have severe disease (odds ratio (OR) 1.40, 95% confidence interval (CI) 1.06–1.85) and airflow obstruction (OR 1.36, 95% CI 1.16–1.59) compared to normal weight asthmatics. Obese asthmatics were not at greater risk for exacerbation (OR 1.41, 95% CI 0.64–3.11) or high treatment burden (OR 1.03, 95% CI 0.83–1.28). **Conclusions.** Obesity is more common than underweight status among children with asthma. Both underweight and obese children with asthma have worse lung function and asthma-related outcomes compared to similar normal weight children, though the phenotypic characteristics of underweight and obese asthmatics differed considerably.

Keywords airflow obstruction, body mass index, forced vital capacity, severity, spirometry

INTRODUCTION

Early life extremes in growth may increase the risk for pediatric asthma (1–3). Obesity and its effect on asthma are areas of intense research; however, many clinically relevant questions remain. Obesity may make asthma more difficult to control (4–10), though the underlying mechanism remains controversial (11–16). Obesity has been reported to worsen asthma symptoms (4–10,17,18), lung function (19–29), hospitalization risk (30), and response to controller medications (31). Exacerbation risk is an important domain determining asthma severity, but the effect of body mass index (BMI)-percentile on exacerbation risk has not been extensively studied in children. In addition, the daily controller therapy (treatment burden) for patients with persistent asthma is a major component of the \$20 billion annual cost of asthma and deleteriously affects patients' quality of life and general adherence (32). The relationships between BMI status and both asthma diagnostic severity and treatment burden have not been clearly defined in children. Since obesity is associated with poor response to asthma therapy, it is rational to hypothesize that obese asthmatics have a greater daily therapeutic

burden, causing obese asthmatics to contribute disproportionately to asthma costs.

Underweight status (BMI < 5th percentile) is also a risk factor for developing asthma but has been understudied in children. Underweight status in children is associated with several chronic diseases (33,34), and in adults it is associated with greater chronic disease mortality (35). Very little is known about the association between underweight status and asthma phenotype in children. Here we report data from a cross-sectional analytic study involving 10,559 children during their initial evaluation at one of four Nemours pediatric subspecialty asthma clinics. We sought to determine the associations between extremes in BMI and asthma severity, risk of exacerbation, lung function, and intensity of controller therapy prescribed by a pediatric asthma specialist.

PATIENTS AND METHODS

The study was reviewed by the Nemours Children's Clinic—Florida Institutional Review Board.

Study Population

We collected initial encounter data on all children referred to one of four pediatric subspecialty asthma clinics within the Nemours health system over a 10-year period between

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2001 and May 2010. Inclusion criteria were age 5–17 years at initial referral and International Classification of Diseases – 9th edition (ICD-9) diagnostic code including intermittent or persistent asthma (EPIC diagnosis codes 493.90BB, BC, B, C, D). In this retrospective electronic chart review, we included only cases with a valid age and BMI and only those cases where the physician used the diagnostic convention (493.90BB/BC, B, C, or D for intermittent, persistent mild, persistent moderate, or persistent severe, respectively) that allowed us to compare diagnostic severity between BMI groups. Other ICD-9 asthma diagnostic conventions such as extrinsic versus intrinsic asthma, chronic obstructive asthma, or cough-variant asthma were not included. We excluded participants with cystic fibrosis, sickle cell disease, cerebral palsy, tracheostomy, or severe developmental or growth delay. Participants with underlying myopathy and muscle weakness on their past medical history were not included in the pulmonary function analysis. Visits occurred at the outpatient and satellite clinics associated with the A.I. DuPont Hospital for Children in Wilmington, Delaware, and the Nemours Children's Clinics in Jacksonville, Orlando, and Pensacola, Florida, and stored within the Nemours Data Warehouse, described previously (20). Each clinic with the exception of Pensacola was affiliated with a regional children's hospital and served as the pediatric pulmonology referral site for its medium-sized US city and environs. The referring areas for Wilmington, Jacksonville, and Orlando came from urban, suburban, and rural settings. Pensacola is a small gulf coast city with rural surroundings and provides subspecialty asthma care for children.

Participants were placed into one of three cohorts based on BMI-percentile computed from the screening height (cm) and weight (kg), according to standard Centers for Disease Control & Prevention (CDC) classification.

Data Collected

From each initial visit, we collected age, sex, race, ethnicity, height, weight, BMI, BMI-percentile, insurance status, all resulting diagnoses, and all medications and doses prescribed by the asthma specialist. The main outcomes included lung function, presence or absence of physician-diagnosis of an asthma exacerbation (ICD-9: 493.91–92), asthma severity given by evaluating physician (intermittent asthma, mild persistent, moderate persistent, severe persistent), and intensity of prescribed therapy by treatment step. Based on the medications prescribed to them as a result of the current visit, each participant was assigned a treatment intensity using the steps recommended in the NHLBI EPR-3's (Expert Panel Report 3) stepwise approach to managing asthma (36). Spirometry values were collected when available including forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and forced expiratory flow between the 25th and 75th percent of FVC (FEF_{25-75}). Spirometry percent-predicted values accounted for sex, age, height, and race. For each participant, we determined the presence or absence of allergic rhinitis (ICD-9: 477.x), food allergy (ICD-9: 693.1,

V15.0), eosinophilic esophagitis (ICD-9: 530.13), and eczema (ICD-9: 692.x).

Data Analysis

Demographics and other study variables were characterized by BMI-percentile group. Quantitative variables were summarized using mean, standard deviation, and number of subjects, while categorical variables were summarized by numbers of subjects and percentages. The chi-square test was used for comparing the distribution of categorical variables between three groups, while one-way analysis of variance (ANOVA) or Kruskal–Wallis test, as appropriate, was used to compare quantitative variables between BMI groups.

ANOVA was performed to compare the mean natural log-transformed spirometry values between three BMI-percentile groups. Variables associated with lung function, exacerbation, treatment intensity, or diagnostic severity in an unadjusted analysis were included in the multivariate model. Additional variables previously associated with asthma or obesity were also included, including sex, age group, and socioeconomic status. The model was adjusted for race, sex, ethnicity, insurance status, age, any atopy, allergic rhinitis, eczema, and asthma severity. The least square (LS) means with standard errors (SEs) and *p*-values were presented. A multivariable logistic regression model was used to assess the associations between BMI-percentile cohort group (and BMI-percentile as a continuous variable) and asthma outcomes (exacerbations, asthma severity, airflow obstruction, treatment level, and inhaled corticosteroid (ICS) dose). Models (except asthma severity) were adjusted for age, sex, race, insurance status, atopy status, asthma severity, and interactions of BMI with age, sex, and race. Because of the possibility of hormonal changes related to puberty changing asthma outcomes, we also evaluated age as a dichotomous variable (5–10 years vs. 11–17 years). Mild airflow obstruction was defined as FEV_1/FVC between 0.80 and 0.84, while moderate obstruction was defined as $FEV_1/FVC < 0.80$. The percent-predicted values for FVC, FEV_1 , and FEF_{25-75} displayed significant variance; therefore we performed pairwise comparisons only on the natural logs of the LS means for each measure. All tests were two-tailed at a level of significance of 0.05. The statistical packages SAS version 9.1.2 (SAS Institute Inc., Cary, NC, USA) and SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) were used for data analyses.

RESULTS

Patient Characteristics

For the study, 10,559 children met the inclusion criteria, with 260 (2.5%) and 2770 (26.2%) qualifying as underweight and obese, respectively (Table 1). Most participants were male (59.4%) and 5–11 years of age (80%). Of patients with a reported race and ethnicity, whites and blacks made up 54.1% and 30.6%, respectively, while 14.3% were Hispanic. Nearly 22% of patients had a

TABLE 1.—Study participant characteristics by weight group.

Variables	BMI-percentile groups			Total patients	P-value
	<5th	5th–95th	>95th		
N (%)	260 (2.5)	7529 (71.3)	2770 (26.2)	10,559	<.001
Age (years)	8.5 (3.4)	8.5 (3.2)	8.9 (3.1)	10,559	<.001
BMI-percentile ^a	1.94 (1.6)	62.02 (25.4)	98.13 (1.4)	10,559	<.001
Age groups					.009
5–11 years	201 (77.3)	6082 (80.8)	2167 (78.2)	8450 (80)	
12–17 years	59 (22.7)	1447 (19.2)	603 (21.8)	2109 (20)	
Gender, n (%)					.215
Male	163 (62.7)	4437 (58.9)	1674 (60.4)	6274 (59.4)	
Female	97 (37.3)	3092 (41.1)	1096 (39.6)	4285 (40.6)	
Race, n (%)					<.001
Caucasian	146 (56.2)	3778 (50.2)	1216 (43.9)	5140 (48.7)	
African-American	66 (25.4)	1975 (26.2)	870 (31.4)	2911 (27.6)	
Other	29 (11.2)	996 (13.2)	426 (15.4)	1451 (13.7)	
Missing/refused	19 (7.3)	780 (10.4)	258 (9.3)	1057 (10.0)	
Ethnicity, n (%)					<.001
Hispanic	22 (8.5)	898 (11.9)	425 (15.3)	1345 (12.7)	
Non-Hispanic	218 (83.8)	5794 (77.0)	2057 (74.3)	8069 (76.4)	
Other/refused	20 (7.7)	837 (11.1)	288 (10.4)	1145 (10.8)	
Comorbidities					
Atopy, n (%)	54 (20.8)	1664 (22.1)	582 (21.0)	2300 (21.8)	.455
Eczema, n (%)	8 (3.1)	175 (2.3)	64 (2.3)	247 (2.3)	.727
Allergic rhinitis, n (%)	52 (20.0)	1581 (21.0)	546 (19.7)	2179 (20.6)	.347
Food allergy, n (%)	0 (0.0)	29 (0.4)	3 (0.1)	32 (0.3)	.051
Clinical site					<.001
Wilmington, DE	107 (41.2)	3754 (49.9)	1500 (54.2)	5361 (50.8)	
Orlando, FL	102 (39.2)	2381 (31.6)	782 (28.2)	3265 (30.9)	
Jacksonville, FL	30 (11.5)	856 (11.4)	287 (10.4)	1173 (11.1)	
Pensacola, FL	21 (8.1)	538 (7.1)	201 (7.3)	760 (7.2)	
Insurance status					<.001
Private only	119 (45.8)	3783 (50.2)	1214 (43.8)	5116 (48.5)	
Medicaid only	89 (34.2)	2467 (32.8)	1071 (38.7)	3627 (34.3)	
Private and Medicaid	20 (7.7)	277 (3.7)	137 (4.9)	434 (4.1)	
None	32 (12.3)	1002 (13.3)	348 (12.6)	1382 (13.1)	
Visit year ^b					
2000–2002	15 (2.4)	474 (75.4)	140 (22.3)	629	<.001
2003–2006	127 (2.7)	3341 (71.0)	1239 (26.3)	4707	
2007–2010	118 (2.3)	3714 (71.1)	1391 (26.6)	5223	

Notes: Values are means (standard deviation) for quantitative variables, and counts (percentages) for categorical variables, unless otherwise indicated. P-values are from one-way ANOVA or non-parametric Kruskal–Wallis test for quantitative variables and chi-square test for categorical variables. BMI, body mass index; DE, Delaware; FL, Florida.

^aAdjusted for age and sex.

^bRow percentages.

comorbid atopic condition (eczema, allergic rhinitis, food allergy) diagnosed besides asthma. Over 13% of children had no documented health insurance, while 52.6% and 38.4% had some form of private or Medicaid insurance, respectively (total > 100% due to some participants having both private and Medicaid coverage).

Obese children were slightly older than the 5th–95th percentile BMI children ($p < .001$). Higher age, African-American race, Hispanic ethnicity, and “Medicaid-only” health coverage were all independently associated with obesity ($p < .05$ for all). Most of the participants were from the Wilmington, Delaware, Nemours/A.I. DuPont clinic. The Wilmington patients had an obesity prevalence that was slightly higher than children from Florida. Underweight status appeared stable over time, while there was a slight increase in obesity prevalence over time (and slight decrease in normal weight prevalence) occurring between 2001 and 2010.

Underweight participants had significantly lower lung function, greater asthma severity, and greater treatment burden (Table 2) compared to normal/overweight participants. Asthma severity was also associated with obesity prevalence ($p < .0001$ for trend) (Figure 1).

Unadjusted Asthma Outcomes among All Participants

Intermittent asthma and persistent asthma made up 21.4% and 78.6% of the cases, respectively. Mild persistent asthma was the most common diagnostic severity (45.3%, 4779/10,559) among all participants. Of the 10,559 cases, 8886 (86.1%) involved prescription of a daily controller medication. While 32% of normal weight patients were given the diagnosis of moderate or severe persistent asthma, the prevalence was 36.4% and 40% for obese and underweight patients, respectively. Similarly, 35% of normal weight patients were prescribed step 4 or higher treatment while 37.5% and 41.2% of obese and

TABLE 2.—Asthma outcomes by weight groups for all participants.

Variables	BMI-percentile groups			Total patients	P-value ^a
	<5th	5th–95th	>95th		
Severity					<.001
Intermittent	43 (16.5)	1647 (21.9)	571 (20.6)	2261 (21.4)	
Persistent mild	113 (43.5)	3474 (46.1)	1192 (43.0)	4779 (45.3)	
Persistent moderate	98 (37.7)	2265 (30.1)	927 (33.5)	3290 (31.2)	
Persistent severe	6 (2.30)	143 (1.9)	80 (2.9)	229 (2.2)	
Exacerbation at time of visit	4 (1.5)	93 (1.2)	38 (1.4)	135 (1.3)	.802
Level of therapy ^b					.004
Step 1	30 (11.8)	989 (13.4)	411 (15.3)	1430 (13.9)	
Step 2	55 (21.6)	1773 (24.1)	559 (20.8)	2387 (23.1)	
Step 3	65 (25.5)	2028 (27.5)	715 (26.6)	2808 (27.2)	
Step 4	37 (14.5)	884 (12.0)	330 (12.3)	1251 (12.1)	
≥Step 5	68 (26.7)	1694 (23.0)	678 (25.2)	2440 (23.7)	

Notes: Values are counts (percentages).

^aPearson's chi-square.

^bLevel of prescribed therapy using the recommended steps from the EPR-3/NHLBI guidelines on management of asthma.

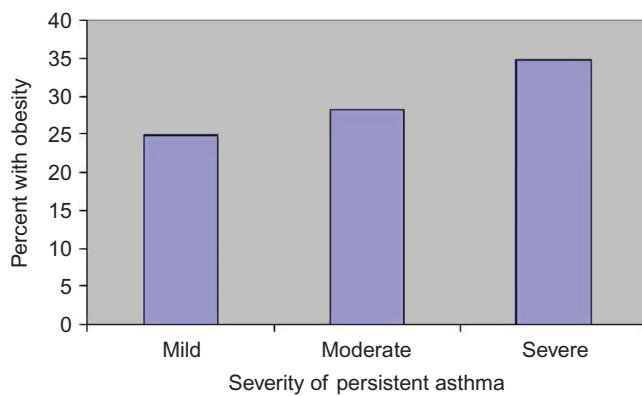


FIGURE 1.—Proportion with obesity by asthma severity. Among asthmatics 5- to 17-year olds seen for an initial visit by an asthma specialist and diagnosed with persistent asthma, we determined the proportion that were obese (BMI-percentile $\geq$ 95th). $P < .0001$ Pearson's chi-square test.

underweight patients, respectively, were prescribed step 5 or higher treatment.

An acute exacerbation, as determined by the treating pediatric asthma specialist, was diagnosed in 1.3% (135/10,559) of the encounters in this cohort over the 10-year study period (Table 2). Weight status did not affect the rate of asthma exacerbation ($p = .802$). BMI-percentile, however, did affect the intensity of treatment prescribed, with both underweight and obese patients being more commonly prescribed higher intensity treatment (based on EPR-3 treatment step, Table 2) in unadjusted analysis.

Lung Function and Airflow Obstruction

A total of 3854 spirometry tests were available for analysis from the 10,559 encounters. In both unadjusted and adjusted analyses, underweight asthmatics had reduced FEV₁ percent predicted (83%) and FVC percent predicted (82.2%) compared to normal weight patients (93.9% FEV₁, 94.8% FVC) (Figure 3). Underweight asthmatics had a greater FEV₁/FVC ratio compared to normal weight asthmatics ($p = .017$). Underweight patients had more

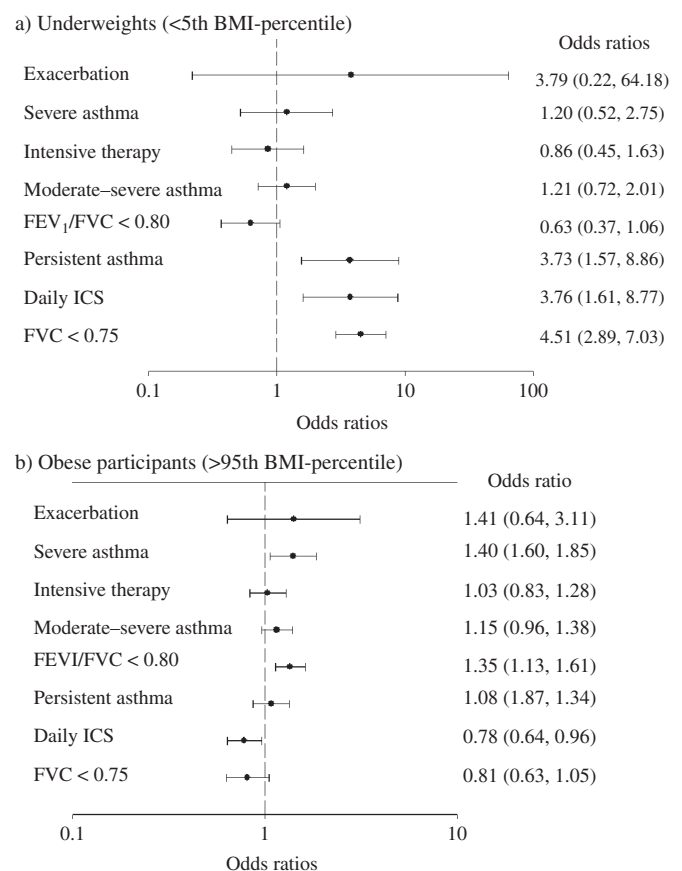


FIGURE 2.—Forest plot of odds ratios for the main asthma outcomes comparing underweight (a) and obese (b) children with the referent normal/overweight children. The odds ratios are displayed with 95% confidence intervals. The analyses were adjusted for gender, race, age group, weight $\times$ age, weight $\times$ gender, weight $\times$ race, age $\times$ weight, insurance status, and asthma severity. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid.

frequent comorbidities with effects on growth and the cardiopulmonary system that may have affected lung function. These included congenital heart disease, tracheo-

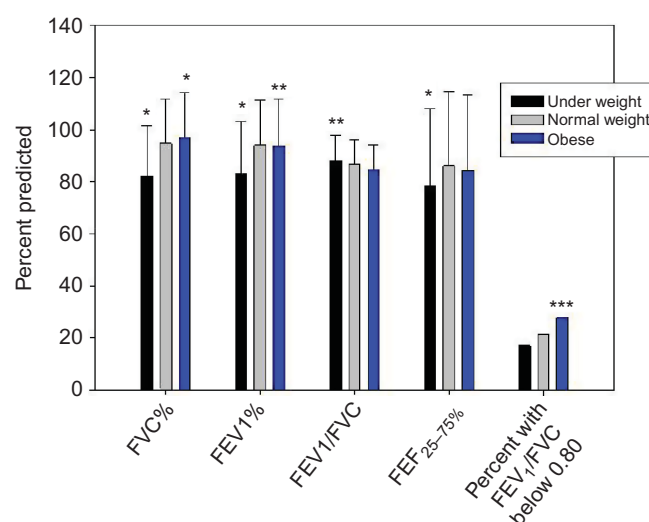


FIGURE 3.—Adjusted mean spirometric measures by weight group. All measures are expressed as percent predicted, except as indicated. FEV₁/FVC is a ratio of the raw values in liters $\times$ 100. Sample sizes ranged between 3817 for FEF₂₅₋₇₅% and 3850 for FVC%. * $p < .01$ for ANOVA pairwise comparison of least square (LS) means with normal weight children after adjusting for gender, insurance, severity, location, and age; ** $p < .05$ for ANOVA pairwise comparison of LS means with normal weight children after adjusting for gender, insurance, severity, location, and age; ANOVA was performed on log-transformed values due to large variance in percent-predicted values; *** $p < .001$ Pearson's chi-square for a difference between groups.

esophageal fistula repair, hypopituitary syndromes, and malabsorption syndromes. However, when these cases were removed from lung function analysis, the lung function impairment among underweight children remained (data not shown).

Obese children were more likely to exhibit moderate airflow obstruction defined as an FEV₁/FVC < 0.80 (odds ratio (OR) 1.345, 95% confidence interval (CI) 1.127–1.605) and overall had mean spirometry values more suggestive of airflow obstruction compared with normal weight children. Though the obstructive impairments in the obese children were modest in degree compared to the restrictive impairment seen among the underweights, the obesity-related lung impairment was significant and affected substantially more children. More than 28% (268/968) of the obese asthmatics had an FEV₁/FVC < 0.80 . We did not see a statistical interaction between age

group and BMI-percentile groups on any of the pulmonary function measures (data not shown).

Obesity was associated with a greater odds for both mild (FEV₁/FVC < 0.85) and more moderate (FEV₁/FVC < 0.80) airflow obstruction, compared to normal or underweight children. Persistent asthma was significantly more likely to occur among underweight asthmatics of all ages (OR 3.729, 95% CI 1.569–8.861) than among normal weights, while underweight asthmatics were also more likely (and obese children *less* likely) to be prescribed ICSs (Figure 2).

Risk Estimates for Asthma Exacerbation

Neither being obese nor being underweight affected the odds of asthma exacerbation among children (Figure 2, Table 2). This lack of effect did not change even after assessing for statistical interaction with age (BMI group $\times$ age group) or race (BMI group $\times$ race). We did not find significant effects of race or the interaction between race and other covariates such as age, age group, and gender on obesity-related asthma outcomes (data not shown).

Asthma Severity and Treatment Burden

Obese children were more likely to be given the diagnosis of severe persistent asthma compared to normal/overweight children (OR 1.397, 95% CI 1.057–1.848). Despite the fact that obese patients were more likely to be given a diagnosis of severe asthma, this did not translate to obese patients being more likely to receive the highest treatment intensity (defined as step 5 or greater) ($p = .784$).

Underweight status was associated with a greater odds for persistent asthma (compared to intermittent only) (OR 3.729, 95% CI 1.569–8.861) and a greater odds of being prescribed a daily ICS medication (OR 3.757, 95% CI 1.608–8.774).

Major Effects

Table 3 summarizes the major findings from the 10,559 children with asthma evaluated by a pediatric asthma specialist. Age, age group, and gender did not affect these main effects.

TABLE 3.—Summary of findings by weight group compared to normal and overweight children.

Outcome	Underweight (<5th BMI-percentile)	Obese (>95th percentile)
Spirometry	Greater restriction in underweights compared to normals ^a	↑Obstruction in obese children compared to normals ^a
Exacerbation risk (ER)	ER not greater in underweights compared to normals ^a	ER not greater in obese children compared to normals ^a
Diagnostic severity	Greater risk for <i>persistent</i> asthma in underweights compared to normals ^a	Greater risk for <i>severe persistent</i> asthma in obese children compared to normals ^a
Treatment burden	Greater risk for daily ICS treatment in underweights compared to normals ^a	No greater risk for high treatment burden ^b in obese children compared to normals ^a

Notes: BMI, body mass index; ICS, inhaled corticosteroid.

^a“Normals” in this comparison include children with BMI from 5th–95th percentile (normal and overweight).

^bDefined as step 5 or greater EPR-3 treatment level.

DISCUSSION

This study, conducted using data from 10,559 asthmatic children evaluated at one of four pediatric specialty clinics, found that the prevalence of low BMI is relatively rare compared to the prevalence of obesity; however, when present, underweight status is most closely associated with significant losses in lung function, greater asthma severity, and higher treatment burden. At the other extreme, obesity, defined as a BMI $\geq$ 95th percentile, was fairly common (26.2% of cases) in this large cohort of children with asthma and was associated with worsening in airflow obstruction and greater odds for severe asthma.

This data set constitutes a large cohort of underweight children with asthma and depicts marked lung function impairment in this group of children. The comorbidity of underweight status among children with asthma is rarely presented in the literature (compared to the field of obesity and asthma) but is important to address, considering the degree of lung function impairment and how this impairment may affect asthma symptom presentation and response to standard treatment. Furthermore, many large asthma trials exclude children with conditions such as past prematurity or growth delay and therefore underweight asthmatics are rarely studied. When impaired body growth occurs during childhood, there appears to be a profound effect on lung size and vital capacity, without a similar impact on airway caliber. Normal spirometry values require sufficient muscle strength, chest wall compliance, and cognitive development. Several diseases with impairment in one or more of these characteristics were seen among our cohort of 260 underweight children. However, when we removed these cases, the degree of lung impairment was reduced among underweight children but was not completely normalized. Any factors affecting growth such as prenatal stress, comorbidities affecting nutritional absorption, and maternal and early life diet are likely to contribute to the lung function patterns seen here in underweight children.

Our study also further confirms that obesity in children with asthma is associated with enhanced airflow obstruction depicted by a reduction in the ratio between FEV₁ and FVC. We and others have shown this type of obesity-related airflow obstruction, but the exact mechanism remains unclear. Other aspects of lung function such as bronchodilator response, airway reactivity, and peak flow variability do not appear to be greater among the obese. Importantly, we found that obesity was not associated with greater risk of asthma exacerbation. Previous reports suggesting that obesity may be associated with greater risk for asthma exacerbations have been from retrospective analyses of treatment decisions performed in the clinical setting rather than based on objective criterion. Past findings of heightened exacerbation risk among obese asthmatics may stem from diagnostic or misclassification bias. We previously showed that peak flow variability, a surrogate for exacerbation risk, was not affected by obesity (37).

We found that obesity was associated with a 40% increased odds of diagnosis with severe persistent asthma. This finding may reflect a true worsening of asthma severity among obese children or could represent diagnostic bias on the part of treating physicians. Obesity could cause the false perception of heightened asthma severity, due to the excess work for the cardiopulmonary system and greater nonspecific respiratory symptoms.

Despite the fact that physicians were more likely to diagnose obese children with severe asthma, they were not more likely to prescribe to the obese children the corresponding highest steps (step 5 or greater) of therapy. This discrepancy between diagnostic severity and level of treatment may be due to several causes. Clinicians may be assigning obese children a higher diagnostic severity due to poor asthma symptom control, but may be unwilling to prescribe elevated therapy due to concerns about age, weight gain, perceived steroid resistance, or non-adherence. Obese children and adults have been reported to be more resistant to ICSs (31,38), which may have deterred some clinicians from increasing the controller dose.

Contrary to our hypothesis, the results of this study suggest that obesity may not be a major contributor to treatment burden and the health-care costs associated with daily controller therapy. Obesity also did not appear to be a risk factor for asthma exacerbation. These findings were surprising to us considering the large power of this study to detect small differences in treatment intensity and exacerbation prevalence. Also, these findings were surprising considering past studies showing greater health-care utilization among obese versus lean asthmatics and considering that the physicians in this study were more likely to give obese patients the diagnosis of severe asthma.

Distinguishing features of this study include a large sample size of children with a broad range of BMI-percentile and asthma severity seen at one of four US cities. All patients were seen and evaluated by a pediatric asthma specialist and received an assessment of asthma severity and given a treatment plan. Limitations of the study include its cross-sectional nature without longitudinal follow-up and the ability to assess response to the therapies prescribed. However, we wanted to focus on how BMI affected a patient's initial evaluation and a provider's assessment of their symptom severity, exacerbation status, and level of controller therapy prescribed.

This analysis was also limited by the completeness of the clinical database. Only about 36% of patients had spirometry values recorded in the EPIC system. This was lower than expected and the lack of data could be due to two general causes. Spirometry may not have been performed at the direction of the treating provider related to young age, poor past performance with the maneuver, or recent disease stability. Second, a lack of data may have occurred because the maneuver was performed but not captured. Regardless of the reason for missing data, an important point is whether or not there is differential information (missing data) bias between the effect groups of interest (i.e., between normal

weights and obese). It is reassuring that the obesity rates of patients with data present and data missing were similar (26.8% vs. 25.2%). Not surprisingly, a comparison of patients with and without spirometry data show a reduced percent of patients prescribed inhaled steroids and higher percent with intermittent disease compared with patients with spirometry data. We might expect that the general severity of those patients not having pulmonary function tests (PFTs) due to doctor's preference might be different from patients who did have PFTs due to more intermittent or stable disease. We were able to address some of the missing data limitations in our statistical approach.

The inclusion criterion for this study was "physician-diagnosed" asthma, which can be a limitation. As Aaron et al. and others have shown, asthma may be overdiagnosed in some physician-diagnosed cohorts (39). This bias may have been reduced in our study due to the fact that patients were seen only at pediatric asthma specialty clinics. Additionally, since our primary variable of interest was weight group, it is important to note that among Aaron's cohort and among another pediatric cohort of asthmatics diagnosed by general practitioners, there did not appear to be a greater misdiagnosis of asthma among the obese compared with normal weights (20,39).

Also, this study involved a specialized cohort of children referred to a pediatric asthma specialist and this fact should be considered when generalizing these results to all asthmatics. Lastly, a primary dependent variable in our analysis was disease severity, determined by individual physician diagnoses. The true accuracy of the diagnostic severity of asthma during routine evaluations is unknown and may be a cause of both misclassification bias and confounding. A higher rate for severe persistent asthma in the obese may be accurate and may reflect a true pharmacologic resistance to steroids that has been reported (40). The higher rate of severe asthma could also be related to a higher dietary fat intake among the obese, which has been shown to impair response to bronchodilation (41).

In conclusion, underweight and obese children both had significantly greater lung function impairments compared to normal weight children, though each was of a different nature. Underweight children had significantly reduced FVC percent predicted and FEV₁ percent predicted consistent with a restrictive impairment compared with normal weight children, while obese children displayed significantly greater airflow obstruction compared to normal weight children. Underweight children were more likely to have persistent asthma and be prescribed therapy involving an ICS. Obese children had a greater likelihood of diagnosis of severe persistent asthma. However, neither obese children nor underweight children were more likely to have had an asthma exacerbation or be prescribed the highest steps of therapy. These outcomes were not changed when stratifying for sex, race, or age.

KEY FINDINGS

Both extremes in BMI-percentile affect characteristics and management of children with asthma. Underweight and

obesity status worsen the asthma phenotype but in different ways. Underweight children had marked reductions in vital capacity, while obese children were more likely to experience airflow obstruction and be diagnosed with severe asthma.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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