

Childhood obesity in pediatric patients with difficult-to-control asthma in a tertiary pediatric subspecialty clinic

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ABSTRACT

Background: Identifying clinical features associated with difficult-to-control asthma will help address overall control and more-effective asthma management.

Objective: To evaluate our clinical observation that the proportion of patients who are overweight or obese is significantly higher in patients with difficult-to-control asthma than in patients with well-controlled asthma.

Methods: This was a retrospective chart review of 400 patients, ages 5 to 18 years. Cases ($n = 200$) were identified as 100 subjects with difficult-to-control asthma and an inhaled corticosteroid dose of ≥ 1000 $\mu\text{g/day}$ and 100 subjects with well-controlled asthma and an inhaled corticosteroid dose of ≤ 500 $\mu\text{g/day}$. The control group included 200 subjects without asthma. Multivariable logistic regression models were used to assess the relationships between asthma status and weight status, age, race, and sex.

Results: The mean body mass index percentile ($\pm$ standard deviation at 95% confidence interval) was significantly higher in the difficult-to-control asthma group versus the well-controlled asthma group versus the control group (74.66 ± 28.19 versus 54.25 ± 29.92 versus 55.19 ± 32.54 ; $p < 0.001$). Thirty-six percent of the difficult-to-control patients with asthma were obese (versus 6% of the patients with well-controlled asthma [$p < 0.001$] versus 13% of patients without asthma [$p = 0.002$]), and 47% normal weight (versus 79% of the patients with well-controlled asthma versus 75% of patients without asthma; $p < 0.001$). The mean age and the proportion of African Americans in the difficult-to-control asthma group were significantly higher than in the well-controlled asthma group and in the control group ($p < 0.001$).

Conclusion: The results of this study demonstrated a significant association between severe persistent difficult-to-control asthma and obesity, age, and race. Patients who are obese and have difficult-to-control asthma need treatment approaches that address both asthma control and weight management.

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More than 6.6 million children in the United States have asthma, and 12.5 million (17%) of U.S. children between the ages of 2 and 9 years are obese. The majority of pediatric asthma patients are well-controlled with anti-inflammatory treatment, such as low doses of inhaled corticosteroids (ICS) (< 500 $\mu\text{g/day}$ fluticasone equivalents). However, ~ 5 –10% of pediatric patients with asthma remain poorly controlled despite treatment with high doses of ICS and systemic corticosteroids.^{1–3} Analysis of study data indicates an important multifactorial link between obesity and

asthma, and indicates that obesity increases the prevalence of asthma and reduces asthma control.^{4–8} Furthermore, prospective studies reported that overweight preceded the later occurrence of asthma symptoms.⁹ The effect of pediatric obesity on asthma severity and control needs to be further evaluated.

It is important to identify clinical features associated with asthma early in life for the development of new interventions to be most effective. According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines,¹⁰ uncontrolled asthma is defined as any of the following criteria: (1) poor symptom control, *i.e.*, Asthma Control Test score of < 20 (or “not well controlled” by National Asthma Education and Prevention Program¹¹ or Global Initiative Asthma guidelines)¹²; (2) frequent severe exacerbations, defined as two or more bursts of systemic corticosteroids (> 3 days each) in the previous year; (3) serious exacerbations, defined as at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year; (4) airflow limitation, *i.e.*, forced expiratory volume in 1 second of $< 80\%$ predicted (in the presence of reduced forced expiratory volume in 1 second/forced vital capacity) after a withhold of bronchodilators.¹⁰ These guide-

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lines also entail that “evidence of any of these four criteria while on current high-dose therapy identifies the patient as having severe asthma.”¹⁰

Our clinical observation in the allergy clinic indicated the hypothesis that the proportion of overweight or obesity is significantly higher in patients with difficult to control (DTC) than in patients with well-controlled asthma.^{10,11} This study was a continuation of two smaller-scale studies by Patel *et al.*¹³ and Sendon *et al.*¹⁴ The study by Patel *et al.*¹³ evaluated medication adherence of 45 pediatric patients with DTC asthma (on ICS of $>1000 \mu\text{g}/\text{day}$). The study compared Asthma Control Test (an adherence estimator questionnaire) and fractional exhaled nitric oxide, and did not identify any significant correlations between poor asthma control and poor medication adherence.¹³ The study by Sendon *et al.*¹⁴ evaluated 100 pediatric patients with uncontrolled asthma (based on NHBLI guidelines)¹¹ for atopy and comorbidities. The study demonstrated that 95% of the patients were atopic based on skin-prick test and/or allergen-specific immunoglobulin E. Twenty-seven percent had tobacco smoke exposure, 47% had sinusitis, 43% had gastroesophageal reflux disease, 55% were overweight, 33% were obese, and 51% had moderate-to-severe airway obstruction based on forced expiratory volume in 1 second.¹⁴ The primary objective of the current study was to evaluate the relationship between being obese or overweight and asthma control.

METHODS

Clinical Data

This was a retrospective chart review of 400 patients, ages 5 to 18 years, who had an allergy clinic visit between May 1, 2013, and March 31, 2014. The sample of cases was collected by performing a query of the medical records for The International Classification of Diseases, Ninth Revision, ICD-9, code for asthma (ICD-9, code 493)¹⁵. The diagnosis of asthma was made by an allergist and was based on symptoms of recurrent episodes of airflow obstruction and spirometry with reversible lower airway obstruction (preversus, postbronchodilator treatment). The classification of asthma severity and control were based on clinical symptoms, the Asthma Control Test, and spirometry according to current guidelines.^{10,11} A review of the correct inhalation technique and medication adherence was a substantial part of every office visit. Patients with gastroesophageal reflux disease were already receiving treatment with proton-pump inhibitors. Exclusion criteria were patients who were <5 years of age or >18 years of age, patients who were not able to adequately perform spirometry, and patients with a non-obstructive pulmonary morbidity (*i.e.*, vocal cord dysfunction or restrictive airflow problems).

Cases ($n = 200$) were identified as 100 subjects with DTC severe persistent asthma and a required high dose of $\geq 1000 \mu\text{g}/\text{day}$ of ICS and 100 subjects with well-controlled mild and moderate persistent asthma and a dose of $\leq 500 \mu\text{g}/\text{day}$ of ICS. A maximum ICS dose of $500 \mu\text{g}/\text{day}$ was chosen for subjects with well-controlled mild and moderate persistent asthma because previous studies showed a maximum achievable benefit for asthma control at a dose of $500 \mu\text{g}/\text{day}$ of ICS.¹⁶ The control group included 200 subjects who did not have asthma and who were seen in one of the allergy clinics for other reasons, such as atopic dermatitis, allergic rhinitis, allergic conjunctivitis, food and drug allergy, and chronic urticaria. In children, the body mass index (BMI) varies with age, sex, and pubertal stage, and, therefore, growth standards are based on BMI percentile.^{17,18} Accordingly, in our study, the subjects' weight status was classified by the BMI percentile for age as normal weight (BMI $< 85\%$), overweight (BMI = $85\text{--}94\%$), or obese (BMI $\geq 95\%$).^{17,18} Age, race, sex, BMI percentile for age, weight status, asthma medication(s), dose of ICS, asthma classification (for cases), and medical history of the control group were transcribed from each subject's medical record and entered directly into a Microsoft Excel (2013) data base. Institutional Review Board and Human Research Committee approval and waivers of consent and authorization to access protected health information were obtained.

Statistical Analysis

The data were analyzed by using SAS 9.4 (SAS Institute, Cary, NC) and SPSS 19 (SPSS Inc., Chicago, IL) software. The level of significance was set at 0.05. Descriptive statistics were reported for all variables stratified by asthma status (well-controlled asthma versus DTC asthma versus controls [without asthma]). After assessing normality, two-sample *t*-tests or analyses of variance were used, when appropriate, to assess differences in age. Analysis of covariance was used to assess differences in BMI percentile for age after adjusting for age. Multivariable logistic regression models were used to assess the relationships between asthma status and race, sex, BMI percentile, or weight status after adjusting for age. *Post hoc* pairwise comparisons with Bonferroni adjustment for type I error were conducted for significant results. In the hypothesis tests for race, Hispanic/Latino, Asian/Pacific Islander, and Other were combined into one category due to the small frequencies. The χ^2 test was used to assess differences in asthma category between the well-controlled asthma and DTC asthma groups.

A power analysis determined that a χ^2 test with one degree of freedom, a total sample size of 200, a significance level of $\alpha = 0.05$, and an anticipated 20% difference in the proportion of patients who are overweight

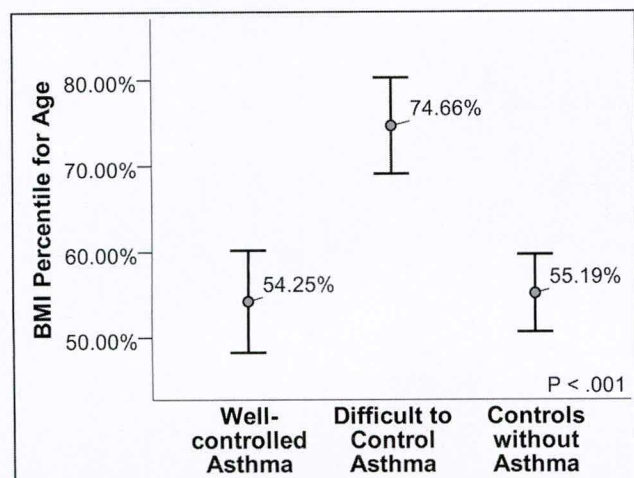


Figure 1. Body mass index (BMI) percentile for age by asthma status. Error bars represent 95% confidence intervals (N = 400).

or obese will have 81% power to detect a statistically significant difference in the proportion of patients who are overweight or obese between the DTC asthma status groups. A total sample size of 400 subjects across two groups (200 asthma patients and 200 patients without asthma), along with a significance level of $\alpha = 0.05$ and an anticipated small effect size Cohen $d = 0.2$, yields 81% power to detect a statistically significant difference in BMI by using the two-sample t -test.

RESULTS

The mean BMI percentile ($\pm$ standard deviation at 95% confidence interval) in the DTC asthma group was significantly higher than in the well-controlled group and in the control group of subjects without asthma after adjusting for age (74.66 ± 28.19 versus 54.25 ± 29.92 , $p < 0.001$; and 74.66 ± 28.19 versus 55.19 ± 32.54 , $p < 0.001$). There was no significant difference in BMI percentile between well-controlled asthma patients and controls without asthma (Fig. 1 and Table 1). There were statistically significantly more normal weight patients ($p = 0.001$) and fewer obese patients ($p = 0.001$) in the well-controlled compared to the difficult to control asthma group. There was no significant difference in weight status between well-controlled asthma patients and controls without asthma. Thirty-six percent of the subjects with DTC asthma were obese (versus 6% of the subjects with well-controlled asthma [$p < 0.001$] versus 13% of subjects without asthma [$p = 0.002$]), 17% were overweight (versus 15% of the subjects with well-controlled asthma [$p = 0.99$] versus 12% of subjects without asthma [$p = 0.26$]) and 47% were normal weight (versus 79% of the subjects with well-controlled asthma versus 75% of subjects without asthma; both $p < 0.001$). (Fig. 2).

The mean age ($\pm$ standard deviation at 95% confidence interval) in the subjects with DTC asthma was

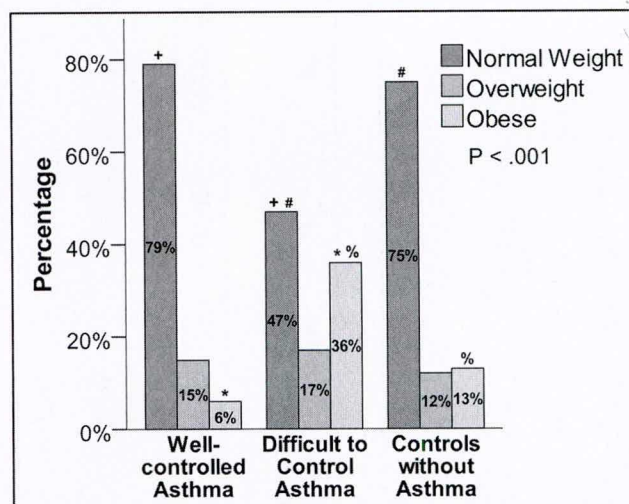


Figure 2. Weight status by asthma status (N = 400); + $p < 0.001$; * $p < 0.001$; # $p < 0.001$; % $p = 0.002$.

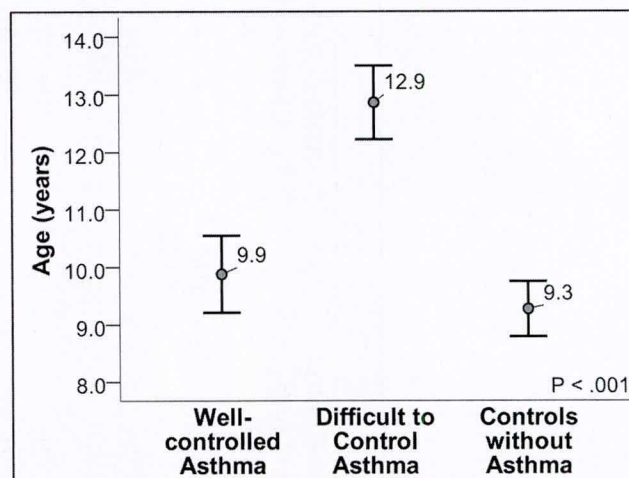


Figure 3. Age by asthma status. Error bars represent 95% confidence intervals (N = 400).

significantly higher than in the subjects with well-controlled asthma and in the control group (12.9 ± 3.2 years in the DTC asthma group versus 9.9 ± 3.4 years in the well-controlled group versus 9.3 ± 3.5 years in the control group [both $p < 0.001$]) (Fig. 3). There was no significant difference in age between the well-controlled asthma patients and controls without asthma ($p = 0.42$) (Table 1). Notably, a significant difference was observed in race between the DTC and the well-controlled asthma groups and the control group after adjusting for age. There were statistically significantly more African Americans ($p < 0.001$) in the difficult to control asthma group compared to patients with well-controlled asthma and controls without asthma ($p < 0.001$). There was no significant difference in race between well-controlled asthma patients and controls without asthma. Seventy-two percent of the subjects with DTC asthma were African American (versus 34%

Table 1 Demographics by asthma status

	Well-Controlled Asthma Group (<i>n</i> = 100)	Difficult-to-Control Asthma Group (<i>n</i> = 100)	<i>p</i> ^a	Asthma Patients Combined (<i>n</i> = 200)	Controls (without asthma) (<i>n</i> = 200)	<i>p</i> ^b	<i>p</i> ^c
Age, mean (SD), y	9.9 ± 3.4	12.9 ± 3.2	<0.001 ^d	11.4 ± 3.6	9.3 ± 3.5	<0.001 ^d	<0.001 ^{e,f}
Race, no. (%)			<0.001 ^{f,g}			<0.001 ^{f,g}	<0.001 ^{f,g}
Hispanic or Latino	5 (5)	4 (4)		9 (5)	5 (3)		
Asian or Pacific Islander	3 (3)	1 (1)		4 (2)	10 (5)		
African American	34 (34)	72 (72)		106 (53)	55 (29)		
White	56 (56)	19 (19)		75 (38)	110 (58)		
Other	2 (2)	4 (4)		6 (3)	11 (6)		
Sex, no. (%)			0.75 ^g			0.94 ^g	0.99 ^g
Boys	58 (58)	57 (57)		115 (58)	117 (59)		
Girls	42 (42)	43 (43)		85 (43)	83 (42)		
BMI percentile for age, mean (SD), %	54.25 ± 29.92	74.66 ± 28.19	<0.001 ^h	64.45 ± 30.75	55.19 ± 32.54	0.0459 ^h	<0.001 ^{f,h}
Weight status, no. (%)			<0.001 ^{f,g}			0.07 ^g	<0.001 ^{f,g}
Normal weight	79 (79)	47 (47)		126 (63)	150 (75)		
Overweight	15 (15)	17 (17)		32 (16)	24 (12)		
Obese	6 (6)	36 (36)		42 (21)	26 (13)		
Asthma category, no. (%)			<0.001 ^{f,i}			—	—
Intermittent	0 (0)	0 (0)		0 (0)	—		
Mild persistent	50 (50)	0 (0)		50 (25)	—		

Table 1 Continued

	Well-Controlled Asthma Group (n = 100)	Difficult-to-Control Asthma Group (n = 100)	p ^a	Asthma Patients Combined (n = 200)	Controls (without asthma) (n = 200)	p ^b	p ^c
Moderate persistent	50 (50)	0 (0)		50 (25)	—		
Severe persistent	0 (0)	100 (100)		100 (50)	—		
SD = Standard deviation; BMI = body mass index.							
^a For well-controlled asthma vs difficult-to-control asthma.							
^b For patients with asthma vs controls without asthma.							
^c For well-controlled asthma vs difficult-to-control asthma vs controls without asthma.							
^d Calculated by using the two-sample t-test.							
^e Calculated by using one-way analysis of variance.							
^f Post hoc pairwise comparisons with Bonferroni adjustment for type I error.							
^g Calculated by using the logistic regression model adjusted for age.							
^h Calculated by using analysis of covariance adjusted for age.							
ⁱ Calculated by using the χ^2 test.							

African American in the well-controlled asthma group and 29% in the control group, both $p < 0.001$), 19% were white (versus 56% in the well-controlled group, and 58% in the control group; both $p < 0.001$). There was no significant difference in sex between the subjects with DTC and with subjects with well-controlled asthma and the control group ($p = 0.99$). The control group of subjects without asthma and the well-controlled asthma group were both significantly different than the DTC asthma group with regard to the subjects' weight status, race, and age (Table 1).

DISCUSSION

In this study, we looked at three groups of subjects, 100 subjects with severe persistent and DTC asthma with a required ICS dose of $\geq 1000 \mu\text{g}/\text{day}$, 100 subjects with mild and moderate persistent and well-controlled asthma with an ICS dose of $\leq 500 \mu\text{g}/\text{day}$, and a control group of 200 subjects who did not have asthma. In a study performed by Holt *et al.*,¹⁴ the maximum achievable benefit for asthma control was at a dose of $500 \mu\text{g}/\text{day}$ of fluticasone. Therefore, for our study it seemed reasonable to choose a dose of $\leq 500 \mu\text{g}/\text{day}$ of ICS for the subjects with well-controlled, mild and moderate persistent asthma. The findings of this study showed a significant relationship between obesity and asthma severity and control. As demonstrated in Fig. 1, the mean BMI percentile ($\pm$ standard deviation at 95% confidence interval) in the severe persistent DTC asthma group was $\sim 20\%$ significantly higher than in the mild and moderate persistent well-controlled asthma group and in the control group of subjects without asthma after adjusting for age ($74.66 \pm 28.19\%$ versus $54.25 \pm 29.92\%$ versus $55.19 \pm 32.54\%$; both $p < 0.001$).

A significantly higher percentage of obesity (36 versus 6%; $p < 0.001$) and a significantly lower percentage of normal weight (47 versus 79%; $p < 0.001$) in the severe persistent DTC asthma group than in the well-controlled mild and moderate persistent asthma group is demonstrated in Fig. 2. The control group of subjects without asthma had a similar percentage of normal weight compared with the well-controlled asthma group (75 versus 79%); both groups had a significantly higher percentage of normal weight than the DTC asthma group (75 versus 79 versus 47%; $p < 0.001$). In addition, the control group had a 23% lower obesity rate than the severe persistent DTC asthma group (13 versus 36%). There was no significant difference among all three groups with regard to the overweight status. These findings were supported by some previous studies that indicated an important link between obesity and poor asthma control.⁴⁻⁸

The mean age ($\pm$ standard deviation at 95% confidence interval) in the DTC asthma group was signifi-

cantly higher than in the well-controlled asthma group and in the control group (12.9 ± 3.2 years in the DTC asthma group versus 9.9 ± 3.4 years in the well-controlled group versus 9.3 ± 3.5 years in the control group [both $p < 0.001$]) are shown in Fig. 3. Subjects with DTC severe persistent asthma were ~ 3 years older than the subjects in the well-controlled asthma group and the control group. The age difference could be attributed to decreased medication adherence in adolescents than in younger children whose medication intake is more closely monitored by their parents. Poor medication adherence was previously demonstrated in a subset of the adolescent population of patients with DTC asthma.¹³ The age difference could also be related to different metabolism and body composition, depending on the age in adolescents versus in younger children.

A significant difference was observed in race between the DTC and the well-controlled asthma groups and the control group after adjusting for age. Seventy-two percent of the subjects with DTC asthma were African American (versus 34% African American in the well-controlled asthma group and 29% in the control group; both $p < 0.001$), 19% were white (versus 56% in the well-controlled group and 58% in the control group; both $p < 0.001$). There was no significant difference in sex among the subjects with DTC and those with well-controlled asthma and the control group ($p = 0.99$). Although, in adults, the link between asthma and obesity is reported to be more strongly related in women, studies in children have been controversial.^{19–22} The subjects' asthma diagnosis was made by an allergist and immunologist based on clinical symptoms and objective measures such as spirometry and/or fractional exhaled nitric oxide. Therefore, despite possible enhanced perception of dyspnea in children who were obese, an overestimation of poor asthma control was reduced by evaluation of data from spirometry and clinical symptoms at the specialist's office visits.

By demonstrating that the control group of subjects without asthma and the well-controlled asthma group were both significantly different than the DTC asthma group with regard to the subjects' weight status, race, and age, our study findings reiterated the association between obesity and asthma severity, race, and age. Nonetheless, to be taken into account was a higher prevalence of obesity in adolescents compared with children ages 6–11 years.²³ Therefore, the differences in age between the subjects with well-controlled asthma and those with DTC asthma can be considered as a limitation of the study. A confounder was poor medication adherence, in particular, in the adolescent population of DTC asthma. Interestingly, part of our study group was evaluated for medication adherence and asthma control. This preliminary smaller-scale

study showed no significant correlation between poor asthma control and medication adherence.¹³ This was a unique study, which looked into several variables that contributed to poor asthma control by combining findings from previous preliminary studies done in our population of subjects with asthma. Our findings supported the significant impact of obesity on poor asthma control in our pediatric asthma population.

CONCLUSION

The results of this study indicated that there was a significant association between severe persistent DTC asthma and obesity, age, and race. The findings of this study underscored the need for innovative multidimensional treatment approaches for the patients with DTC asthma by addressing both asthma control and weight management.

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