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Effect of inhaled corticosteroid use on weight (BMI) in pediatric patients with moderate-severe asthma

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ABSTRACT

Objectives: Assess the relationship between inhaled corticosteroid use (ICS) and weight (BMI) in pediatric patients with moderate-severe asthma. Assess if the number of emergency department (ED) visits correlates with overall BMI trajectory. Assess the trend of prescribing biologic therapy in pediatric patients with moderate-severe asthma and determine its relationship with weight (BMI). **Methods:** A retrospective chart review was performed on 93 pediatric patients with moderate-severe asthma to determine the relationship between ICS use and weight (BMI), biologic therapy and BMI, and number of ED visits and BMI trajectory. A mixed effects model was employed with the correlation between repeated measures accounted for through the random effects. **Results:** There is a statistically significant increase of 0.369 kg/m² in BMI trajectory per year in subjects on high-dose steroids compared to an increase of 0.195 kg/m² in the low dose group ($p < 0.05$). The BMI of subjects initiated on biologic therapy (omalizumab or mepolizumab) had a statistically significant decrease in BMI trajectory of 0.818 kg/m² per year ($p < 0.05$). Subjects with ≥ 5 ED visits due to asthma exacerbations had a significantly higher BMI trajectory ($p < 0.05$). **Conclusions:** The potency of ICS use in pediatric patients with moderate-severe asthma affects BMI trajectory; the higher the dose, the greater the projected BMI increase per year. Initiation of biologic therapy decreased BMI trajectory over time. Lastly, those with frequent ED visits had a higher BMI trend. Future prospective studies are warranted that further evaluate the potential metabolic impacts of ICS and assess the effects of biologic therapy on BMI.

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Biologic therapy; BMI trajectory; mepolizumab; omalizumab; uncontrolled pediatric asthma

Introduction

Asthma is one of the most common significant chronic diseases that affects children and consequently, is a major global health concern (1). It is a disease characterized by airway inflammation that is mediated by an excessive allergic immune response in most pediatric asthma cases. At present most patients with moderate-severe asthma require long-term, daily nonspecific medication such as corticosteroids in combination with a second controller such as a long acting beta-2 agonist to control the underlying inflammation and prevent symptoms and life-threatening asthma attacks (2). Although moderate-severe persistent asthma is relatively less common, affecting approximately 5% of childhood asthma cases (3), studies report that those with moderate-severe asthma have significantly higher healthcare costs than those with mild asthma (4–6). These increases in costs for both moderate and severe asthma patients are largely due to frequent ED visits and hospitalizations (4,7).

To date, there is no known cure for asthma. Most commonly, moderate-severe childhood asthma is treated following guideline based drug therapy based primarily on data from adult studies, involving higher-dose inhaled or oral corticosteroids combined with long acting beta-2 agonists and other add on therapies (2,8). However, in a fraction of cases suffering from the moderate-severe form of asthma, the disease is refractory to even high doses of steroids and a second controller. In these uncontrolled patients, the required steroid-based treatment leads to significant side effects and compromises the patient's quality of life. For pediatric patients on inhaled corticosteroids (ICS), multiple studies have demonstrated a decrease in linear growth by up to 1 cm per year (9,10). Furthermore, suboptimal adherence to daily controller medications has been shown to result in increased risk of hospital admission (11) and poor disease control (12).

Despite a high degree of heritability in pediatric asthma, external factors such as obesity can affect disease

risk. Obesity, as defined by body mass index (BMI), is a serious public health problem and is associated with reduced quality of life, increased healthcare costs, and increased risk for several chronic diseases including asthma. Over the recent decades, the change in obesity prevalence has been greatest among children (13). Not only is obesity a risk factor for moderate-severe asthma (14), but obesity in children with asthma is associated with greater airflow obstruction and a diminished response to ICS, often leading to the use of frequent systemic steroids (15). Therein lies a potential vicious cycle—obesity disposing patients to moderate-severe asthma; treatment for moderate-severe asthma with corticosteroids leading to obesity. The relationship between oral systemic steroids and weight has been well established as well as the relationship between oral systemic steroids and height in children (9,10). However, there is still limited knowledge about the relationship between ICS use and weight in pediatric patients. Studying this relationship can help guide therapy in patients with moderate-severe asthma by deterring the use of more frequent and higher doses of corticosteroids and turning to different forms of treatment such as biologic therapy.

In recent years, biologics, which encompass genetically designed and expressed proteins that target asthma-specific endogenous immunological processes, have become available for pediatric patients with asthma. Two biologics currently recommended for consideration in pediatric severe asthma are omalizumab and mepolizumab (16). In a randomized trial of 400 pediatric participants, omalizumab (anti-Immunoglobulin E) decreased the number of exacerbations by almost 20% and reduced the amount of inhaled glucocorticosteroid dose by 109 mcg/day compared to placebo (17). Further, in a recent “real world” observational study omalizumab was shown to decrease exacerbation frequency in patients with moderate-severe asthma with reported improved quality of life and asthma control (18). In those older than 12, mepolizumab (anti-IL5), nearly halved the amount of exacerbations in those with refractory eosinophilic asthma compared to placebo in a study with 621 participants (19). Biologic therapy may be an appropriate treatment option for patients with moderate-severe persistent asthma whose symptoms are inadequately controlled with high-dose ICS.

In our study, we aimed to determine if there is a relationship between ICS use and BMI in children with moderate-severe asthma. Additionally, we assessed the trend of the BMI trajectory of patients who were prescribed biologic therapy, omalizumab, or mepolizumab. As a secondary outcome, we assessed if

the number of ED visits correlated with overall BMI trajectory.

Methods

The University of California, San Diego Institutional Review Board-approved retrospective chart review was performed on 93 patients of the Severe Asthma Clinic at Rady Children’s Hospital. Eligible patients for review were 18 months to 18 years of age, diagnosed with moderate-severe asthma, prescribed ICS, and seen by the clinic during the period of 09/15/2011 to 08/24/2016. Patients with at least two clinic visits were included with visits on average every 3–6 months. Moderate-severe asthma patients were defined as patients with asthma that were not controlled on high-dose ICS, or required frequent systemic steroids to remain controlled (8). Lack of control is defined as requiring two or more emergency room visits, hospitalization in the last year, or systemic steroid use due to asthma exacerbation (20). The patient’s medical record was obtained using the electronic medical record, EPIC. BMI was used as a measure of patient’s weight to normalize for children’s height and weight with age.

Demographic variables (age, sex, height, weight, BMI, and BMI percentile), ICS and doses, duration of therapy, montelukast use, oral steroid administrations, and whether the patient transitioned to omalizumab or mepolizumab were collected. The number of ED visits was also collected for secondary outcome analysis. The potency of ICS for each patient was categorized as “low,” “medium,” or “high” based off the estimated comparative daily dosages adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (2). Statistical significance for variables compared by ICS potency was determined by ANOVA for continuous variables and Fisher’s exact test for categorical variables.

A linear mixed-effects model was used to model individual BMI trajectories (longitudinal differences) in identifying factors associated with BMI change over time. Both individual patterns of change (individual random effects) and population averages (fixed effects) are estimated. A dependent random intercept and slope over time is included to account for correlation among repeated measures. Fixed effects included steroid classification (low/medium/high as determined by the National Asthma Education and Prevention Program: Expert Panel Report 3), age at BMI measurement, their interaction, gender, whether the subject was on biologic therapy, and the interaction of this variable with age at measurement. For steroid classification as a three level categorical

Table 1. Patient characteristics.

	Steroid classification			Overall	p-value
	Low	Medium	High		
Age at first visit (years)	<i>n</i> = 31 4.69 ± 3.31 (3.47, 5.90)	<i>n</i> = 15 6.98 ± 4.02 (4.76, 9.21)	<i>n</i> = 47 7.77 ± 4.42 (6.36, 9.18)	<i>n</i> = 93 6.62 ± 4.42 (5.71, 7.53)	0.067
Gender	<i>n</i> = 31	<i>n</i> = 15	<i>n</i> = 47	<i>n</i> = 93	
Female	13 (41.9%)	6 (40.0%)	20 (42.6%)	40 (41.2%)	1.000
Male	18 (58.1%)	9 (60.0%)	27 (57.4%)	57 (58.8%)	
BMI (pre)	<i>n</i> = 29 18.21 ± 4.13 (16.64, 19.78)	<i>n</i> = 14 20.61 ± 5.76 (17.29, 23.94)	<i>n</i> = 45 19.55 ± 5.25 (17.97, 21.21)	<i>n</i> = 88 19.28 ± 5.01 (18.21, 20.34)	0.178
BMI (last)	<i>n</i> = 30 18.79 ± 5.37 (16.79, 20.80)	<i>n</i> = 15 22.42 ± 6.59 (18.61, 26.22)	<i>n</i> = 44 22.36 ± 7.14 (20.19, 24.53)	<i>n</i> = 88 21.15 ± 6.65 (19.74, 22.56)	0.086
BMI percentile (pre)	<i>n</i> = 25 66.78 ± 31.61 (53.75, 79.83)	<i>n</i> = 14 69.71 ± 36.02 (48.91, 90.50)	<i>n</i> = 40 63.00 ± 33.91 (52.15, 73.85)	<i>n</i> = 79 65.39 ± 33.25 (57.94, 72.83)	0.802
BMI percentile (last)	<i>n</i> = 30 70.77 ± 27.63 (60.46, 81.09)	<i>n</i> = 13 69.39 ± 33.83 (48.94, 89.83)	<i>n</i> = 43 68.90 ± 32.81 (58.80, 79.00)	<i>n</i> = 86 69.63 ± 30.90 (63.00, 76.25)	0.898
Follow up (years)	<i>n</i> = 31 1.73 ± 1.58 (1.15, 2.31)	<i>n</i> = 14 3.00 ± 1.82 (1.94, 4.05)	<i>n</i> = 44 3.30 ± 1.94 (2.70, 3.89)	<i>n</i> = 89 2.70 ± 1.93 (2.30, 3.11)	0.035*

Continuous data are presented as mean (standard deviation), while categorical data are presented as count (percentage). Significance is determined by ANOVA for continuous variables and Fisher's exact test for categorical variables.

covariate and its interaction with time, we include an F test to determine overall significance. A significance level of $p < 0.05$ was used.

Results

Our study reveals several significant findings. Firstly, the BMI of subjects on high potency ICS increased by 0.369 kg/m² per year compared to those on low potency ICS ($p = 0.008$). Next, we saw a reversal of this trend in subjects on biologic therapy with a decrease in BMI of 0.818 kg/m² per year ($p = 0.023$). Finally, the BMI trajectory was 0.573 kg/m² higher ($p = 0.023$) in those with greater than or equal to five ED visits compared to those with less than five ED visits.

Patient characteristics were essentially the same across the comparison groups except the amount of follow-up in years, as one would expect ($p = 0.035$). The number of years of follow up increases from low (1.73 years, 95% CI: [1.15, 2.31]) to medium (3.00 years, 95% CI: [1.94 to 4.05]) to high (3.30 years, 95% CI: [2.70, 3.89]) steroid classifications (Table 1).

Overall, BMI increases over time regardless of steroid classification (Figure 1). Taking a closer look into the rate of rise of the BMI over time, the BMI trajectory of the “high” potency steroid group is higher than those of “medium” and “low” classifications. In the “high” potency group, the BMI begins with the lowest BMI but around age 5, increases at a rate greater than either the “medium” or “low” groups.

There is a statistically significant increase in BMI trajectory in subjects on “high” potency steroids as compared

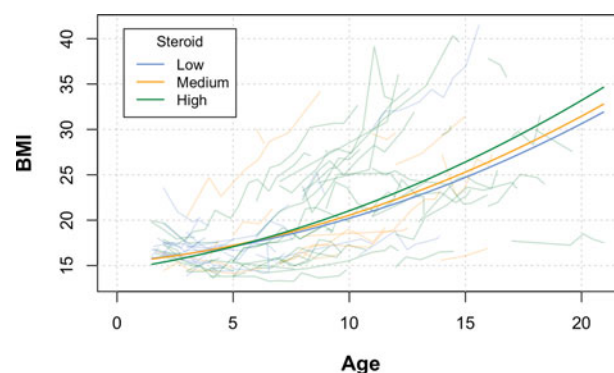


Figure 1. BMI values over time distinguished by steroid potency classification. Regression lines superimposed on the raw BMI trends.

to “low” potency groups ($p = 0.008$) and “low/medium” groups ($p = 0.441$) (Table 2). The BMI trajectory in the “low” steroid classification increases at a rate of 0.195 per year (95% CI: [−0.192, 0.582]). Compared to the “low” group, the BMI trajectory of those in the “medium” steroid classification increases at a rate 0.048 more than the “low” group (95% CI: [−0.075, 0.171]). This increase

Table 2. Mixed model output for BMI with covariates for steroid classification, time, their interaction, age, and gender.

	Rate of raw BMI increase/year	95% CI	p value
Low potency—reference	0.195	(−0.192, 0.582)	0.325
Medium potency	0.243	(−0.075, 0.171)	0.441
High potency	0.369	(0.046, 0.302)	0.008*

Controlled for quadratic term for age, controlled for gender. The confidence limits for medium and high potency relate to the difference from the reference category.

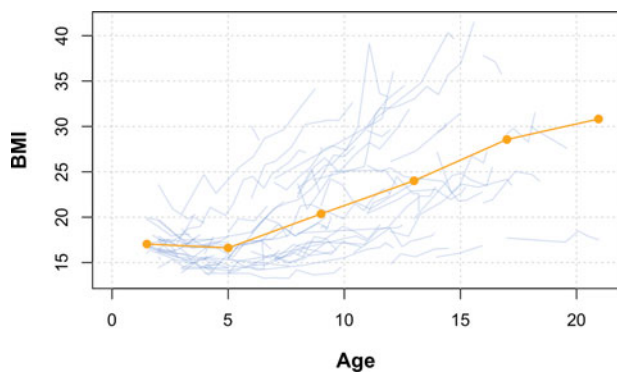


Figure 2. Piecewise regression lines from model in Table 3, superimposed on the raw BMI trends.

between “low” and “medium” is not statistically significant ($p = 0.441$). However, the BMI trajectory of those in the “high” group increases at a rate of 0.174 as compared to the “low” group (95% CI: [0.046, 0.302], $p = 0.008$).

When looking at the rate of BMI increase per year for different age groups, there is a statistically significant difference in rate of BMI increase per year for the age group 5–9 years ($p = 0.001$) (Table 3). From age 18 months to age 5, there appears to be a decrease in BMI over time. However, starting at age 5, BMI trajectories begin to increase and increase thereafter. The increase is highest between age 5–9 and lowest between age 17–21.

Figure 2 depicts regression lines from Table 3, superimposed on raw BMI trends. The regression line follows a normal growth curve in that from age 0 to 5, BMI decreases and then increases starting at age 5 with the steepest increase immediately after age 5. When comparing to CDC BMI-for-age growth charts, our regression line falls within the 50th percentile at age 5. By age 10, our regression line increases into above the 90th percentile and remains above the 90th percentile thereafter until age 20, suggesting between age 5 and 20, patients were in the overweight category (85th to less than 95th percentile).

Five patients were transitioned to biologic therapy, four to omalizumab and one to mepolizumab. We found that patients who switched to biologics had a statistically significant decrease in BMI trajectory per year (Table 4)

Table 3. Piecewise-linear regression for age changes over time (4-year intervals). Each row corresponds to the slope over that time period, while the p value corresponds to the change in slope compared to the previous age group.

	Rate of raw BMI increase/year	95% CI	p value
Age 0–5	−0.122	(−0.432, 0.188)	0.441
Age 5–9	0.937	(0.679, 1.196)	<0.001*
Age 9–13	0.912	(0.623, 1.202)	0.892
Age 13–17	1.137	(0.761, 1.513)	0.314
Age 17–21	0.573	(−0.120, 1.265)	0.135

Table 4. Mixed model output for BMI with covariates for biologic therapy, time, age, and gender.

	Raw BMI rate of change/year	95% CI	p value
Biologic therapy × time (years)	−0.818	(−1.520, −0.116)	0.023*

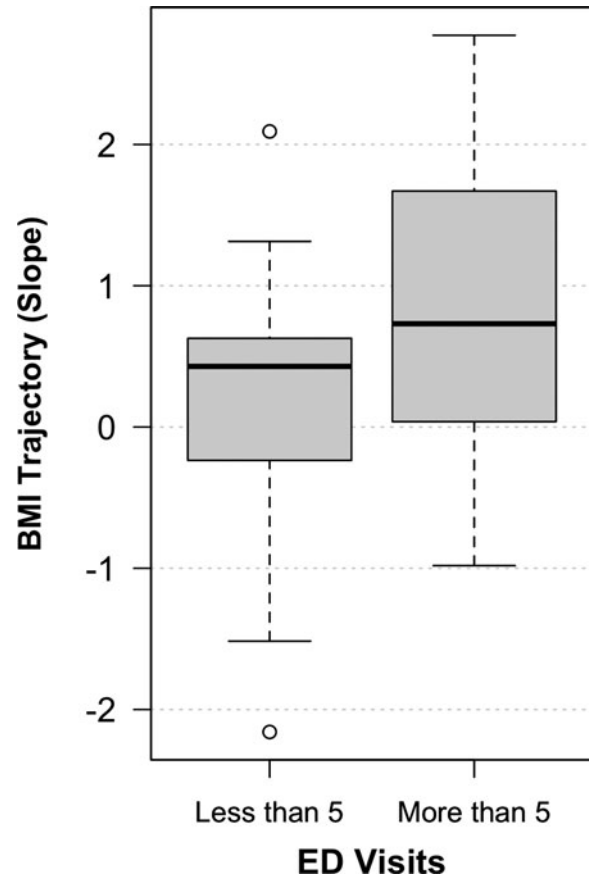


Figure 3. Boxplot of BMI trajectories (slopes) by number of ED visits.

(−0.818 kg/m² per year, 95% CI: [−1.520, −0.116], $p = 0.023$).

We compare the overall BMI trajectory per subject with their total number of ED visits. Only subjects with at least 1 year of follow up are included. When controlling for the subjects age at first visit, we find a significantly higher BMI trend in subjects who have had more than five ED visits due to asthma exacerbation ($p = 0.022$) (Figure 3).

Discussion

The statistically significant increase in BMI trajectory in subjects on “high” potency ICS as compared to “low” potency group ($p = 0.008$) and “low/medium” potency groups ($p = 0.011$) suggests that the amount of ICS a patient receives affects BMI over time. Pediatric patients

with moderate-severe asthma who are on “high” potency ICS have a greater increase in BMI over time. For those who are already overweight or obese, use of high dose ICS would exacerbate their obesity and because of their obesity, would require higher doses of ICS.

Absolute BMI values were chosen over BMI percentiles for the analysis as we felt this measurement was more applicable to our study population. Specifically, CDC BMI percentiles and cut-offs for age may be biased in more diverse populations, as seen at our institution.

Further, we see from the piecewise regression for age changes over time (4-year intervals) that starting at age 5, BMI trajectories begin to increase and increase thereafter. This regression line mimics the CDC BMI-for-age growth chart and upon comparison, our regression line is consistently above the 90th percentile beginning age 9, effectively being placed into the “overweight” category. Age 5–9 may be a particularly susceptible window for this to occur. This affirms our hypotheses that obesity and asthma are associated with one another in that obesity makes moderate-severe asthma harder to control and uncontrolled moderate-severe asthma warrants higher doses of ICS, potentially leading to more obesity.

The decrease in BMI trajectory over time with the conversion from ICS to biologics provides valuable insight in considering the initiation of biologic therapy in the future. The use of biologics may improve treatment adherence with its biweekly or monthly injections, circumventing the challenge of daily adherence with ICS (21). Patients with a history of nonadherence to their ICS medications have shown improvement in adherence with omalizumab in the literature (22) as well as a decrease in daily inhaled corticosteroid dosage (17). Although studies that link inhaled corticosteroids to increased BMI are limited, there are several that have linked oral steroid courses with increased BMI (23). Specifically, researchers found in a recent study that adults who received ≥ 4 prescriptions for oral corticosteroids were more likely to have obesity as a new diagnosis ($p < 0.01$) (24,25). It is therefore possible that increased medication adherence and decreased cumulative steroid exposure may lead to a decrease in BMI. However, due to our small sample size ($n = 5$), our study was not powered to make definitive conclusions or therapeutic recommendations. Projected over a longer study period and with a larger sample size, this BMI trend could be clinically significant.

One of the main reasons for considering biologic therapy in pediatric patients with moderate-severe asthma is lack of control on high dose ICS alone. However, these medications can be cost-prohibitive. The incremental lifetime direct medical cost from the perspective of a

10-year-old obese child relative to a 10-year-old normal weight child ranges from \$12,660 to \$19,630 when weight gain through adulthood among normal weight children is accounted for. Multiplying the lifetime medical cost estimate of \$19,000 times the number of obese 10 year olds today generates a total direct medical cost of obesity of roughly \$14 billion for this age alone (26). By decreasing utilization associated with frequent ED visits and the cost of managing obesity, initiation of biologics may become a more cost-effective option.

In our study, we find that there is a statistically significantly higher BMI trajectory in subjects who have had more than five ED visits due to asthma exacerbations ($p = 0.025$). This suggests a lack of control of their asthma on their current asthma medication regimen. Gaining and maintaining control of asthma, with perhaps biologic therapy, could decrease ED visits and consequently, decrease direct medical costs including ED admits, hospital admissions, and ED medication use. Thus, BMI should be a consideration when evaluating therapeutic options for asthma management from both a clinical outcomes and health utilization standpoint.

Some limitations of our study are associated with the nature of our study method. The retrospective chart review provided incomplete data regarding the start and end dates for ICS medications. Relevant data before the start of the study date could not be collected for analysis. Inherent selection bias is present as we only analyzed patients of the Severe Asthma Clinic at Rady Children's Hospital, a multidisciplinary academic center. This possibly limits the generalizability of our results to the general asthma population. The sample size for those on biologic therapy was low ($n = 5$). Due to the constraints of the study period duration, the true effect of biologics on BMI may not have been captured. Other confounding factors such as patient lifestyle with food, diet, and exercise could not be controlled due to the nature of a retrospective study. Factors such as socioeconomic status, parent and child education level, medication literacy, and access were treated as constant for the duration of the two-year study. As such, the decrease in BMI after initiation of biologics provides an interesting trend but one that requires further prospective larger scale studies. Additionally, subjects could only initiate biologic therapy if they were ≥ 12 years old and the inherent BMI trajectory in this age group should be considered. Further, a limitation in modeling age and time in observational longitudinal data is selection or recruitment bias in that participants recruited at an older age may be different from participants who were recruited at a younger age and remained in the study to become older persons.

Further studies looking at the effect of biologics on BMI trajectory for a longer duration of time with larger sample sizes would help elucidate the comprehensive effect of biologics. In addition, cost-effectiveness analysis with biologic asthma therapy could help provide an alternative treatment option for patients with refractory moderate to severe asthma in a cost-effective manner.

Conclusion

To our knowledge, this is the first study in children that has examined BMI trajectory as a major endpoint for the use of ICS. This study reveals that the potency of ICS in pediatric patients with moderate-severe asthma affects BMI trajectory; the higher the dose, the greater the projected BMI increase per year. Furthermore, those with frequent ED visits were also noted to have a higher BMI trend. Lastly, in a small sample size, initiation of biologic therapy decreased BMI trajectory over time. These findings warrant larger prospective investigation.

Conflicts of interest

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

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