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Overweight/obesity status in preschool children associates with worse asthma but robust improvement on inhaled corticosteroids

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Abstract

BACKGROUND: Overweight/obesity (OW) is linked to worse asthma and poorer inhaled corticosteroid (ICS) response in older children and adults.

OBJECTIVES: Describe the relationships between OW and asthma severity and response to ICS in preschool children.

METHODS: This post-hoc study of three large multi-center trials involving 2–5 year-old children compared annualized asthma symptom days and exacerbations among normal weight (NW) (body mass index (BMI) 10–84th percentile) versus OW (BMI ≥85th percentile) participants. Participants had been randomized to daily ICS, intermittent ICS or daily placebo. Simple and multivariable linear regression was used to compare BMI-groups.

RESULTS: Within the group not treated with a daily controller, OW children had more asthma symptom days (AD) (90.7 vs. 53.2, p=0.020) and exacerbations (1.4 vs. 0.8, p=0.009) compared to NW children. Within the ICS-treated groups, OW and NW children had similar AD (daily ICS: 47.2 vs. 44.0 days, p=0.44; short-term ICS: 61.8 vs. 52.9 days, p=0.46; as-needed ICS: 53.3 vs. 47.3 days, p=0.53), and similar exacerbations (daily ICS: 0.6 vs 0.8, p=0.10, short-term ICS: 1.1 vs 0.8 days, p=0.25; as-needed ICS: 1.0 vs 1.1, p=0.72). Compared to placebo, daily ICS in OW led to fewer annualized asthma symptom days (90.7 vs. 41.2, p=0.004) and exacerbations (1.4 vs. 0.6, p=0.006), while similar protective ICS effects were less apparent among NW.

CONCLUSION: In preschool children off controller therapy, OW is associated with greater asthma impairment and exacerbations. However, unlike older asthmatics, overweight/obese preschool children do not demonstrate reduced responsiveness to ICS therapy.

Capsule Summary:

Overweight/obesity in preschoolers is associated with greater asthma symptom days and exacerbations when off controller therapy, and an overall good response to inhaled corticosteroids.

Keywords

Asthma; Overweight; Obesity; Children; Infants; Exacerbation

INTRODUCTION

Asthma is one of the most common chronic diseases of childhood and adolescence(1, 2). High body mass index (BMI) status has a poorly defined relationship with asthma severity. According to national asthma guidelines, classification of asthma severity in controller-naïve patients depends on (1) impairment of daily functioning by asthma symptoms and (2) risk of exacerbations(3). Studies involving older youths and adults have found that overweight or obesity status (OW) worsens asthma symptoms(4–6), asthma-related healthcare utilization(6–8) and response to inhaled corticosteroids (ICS)(9–11). For example, Quinto studied 32,321 children aged 5–17 years within the Kaiser Permanente health system and found that OW was associated with poor asthma control and exacerbations, measured by rescue inhaler and oral steroid dispensing, respectively(6). However, others have found no association between OW and measures of asthma severity(12–14), or found that high BMI was associated with reduced (not greater) airway hyperresponsiveness, a central component of asthma(15–17). Very little data currently exist exploring the effects of OW status on asthma severity in preschool children. In addition, no studies to our knowledge have investigated OW and ICS-response in preschoolers. The lack of research of OW status in preschoolers is an important gap in children's health considering that preschool children (< age 5 years) are at a particularly high risk for morbidity stemming from asthma or recurrent wheezing. Half of all children experience wheezing by age 5(18), roughly one-third of preschool children suffer prolonged episodes of recurrent asthma symptoms(19), and among preschoolers, asthma symptoms are a leading cause of hospitalizations and ED visits. Additionally, the current prevalence of OW in the United States for 2–5 year olds is 27%(20). Elucidating the factors in preschool children which affect the treatment efficacy of ICS is of particular public health interest. If early life OW status does worsen asthma symptoms and reduces the effectiveness of inhaled corticosteroids, early life nutrition and obesity prevention efforts could become a critically important intervention.

Currently, ICS are the most effective single anti-asthma controller medication available for the prevention of daily symptoms and exacerbations. Therefore, response to daily ICS is an important phenotypic characteristic of childhood asthma. Only a few studies in adults and one study in older children(11) have evaluated the effect of OW on ICS treatment response. Studies have demonstrated a reduced response to ICS among adults with high BMI(9, 21, 22). In the Childhood Asthma Management Program (CAMP) study, Forno and colleagues found that OW children demonstrated a reduced improvement in lung function and asthma-related urgent care use(11) in response to ICS compared to NW children. Using data from three large prospective trials of preschool children enrolled in the Childhood Asthma Research and Education (CARE) and AsthmaNet networks, we evaluated the effects of early life OW-status on prospectively determined asthma symptom days and exacerbations in children treated with either ICS (daily or intermittent step-up) or placebo. We hypothesized

that among both placebo-treated and ICS-treated children, OW status would lead to greater AD and exacerbations.

METHODS

Participant Selection

Details of the main studies (Individualized Therapy for Asthma in Toddlers (INFANT), Prevention of Early Asthma in Kids (PEAK), and Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) have been published (23–26). All caregivers of participants signed written informed consents. The present post-hoc study was approved by the Nemours (928923–2) institutional review board. We included baseline and intervention period data from 736 preschool aged participants (24–59 months) with mild persistent asthma or recurrent wheezing who were randomized into one of three multi-center placebo-controlled trials in which they received either daily ICS, intermittent ICS or placebo. Weights were determined using a calibrated electronic or beam balance scale. Standing height was measured without shoes using a calibrated stadiometer accurate to the nearest millimeter. Age and sex-adjusted body mass index percentiles were calculated using a centralized calculator using CDC growth chart data. Because underweight children have also demonstrated more severe asthma(27), participants with a body mass index (BMI) percentile < 10^{th} percentile were excluded in this analysis.

The INFANT study was a multicenter, randomized, double-blind, double-dummy, clinical trial in children 12–59 months (n=300) with persistent asthma, which was factorially linked to the Acetaminophen versus Ibuprofen in Young Children with Asthma (AVICA) study. Because treatment with ibuprofen compared to acetaminophen did not affect asthma outcomes (28), we included INFANT data in the combined analysis. INFANT participants completed a 2–8 week run-in period followed by three 16-week crossover intervention periods with daily ICS (fluticasone propionate, 88μg twice daily, GlaxoSmithKline), daily LTRA (montelukast, 4 mg by mouth, Merck and Co., Inc.), and intermittent “as-needed” ICS treatment (fluticasone propionate, 88μg given given whenever 2 inhalations of albuterol sulfate are needed, GlaxoSmithKline). The PEAK study was a multicenter double-blind two-arm parallel study that randomly assigned 285 participants 2–3 years of age with a positive modified asthma predictive index to treatment with either fluticasone propionate (GlaxoSmithKline) 88μg twice daily or masked placebo for 24 months. The MIST trial was a multi-center randomized double-blind parallel trial which studied 278 children between the ages of 12 and 53 months who had recurrent wheezing and a positive modified asthma predictive index. Participants were randomly assigned to receive a budesonide inhalation suspension (Pulmicort Respules, Astra-Zeneca) for 12 months as either a daily low-dose ICS (0.5 mg nightly) or an intermittent “short-term” ICS (1 mg twice daily for 7 days, starting early during a predefined respiratory tract illness).

Clinical Data

We analyzed demographics, medical and environmental histories, and asthma-related utilization among 736 participants from the three trials who were older than 24 months at enrollment. Intervention period data were collected ranged over a 14-year period (PEAK

2001–2004; MIST 2008–2010; INFANT 2013–15). Participants were classified as normal weight (10–84th percentile BMI)(NW) or overweight/obese (OW) (≥85th percentile BMI) based on BMI percentiles according to the Centers for Disease Control and Prevention classification(29). Figures show asthma symptom days and exacerbations by quartiles to demonstrate the lack of a BMI-percentile trend and to justify combining percentiles 10–84 into one group. Aeroallergen testing was performed by skin prick testing or blood ImmunoCAP (Phadia AB, Uppsala, Sweden) allergen-specific IgE.

During the intervention period, the impairment domain of asthma severity was measured by annualized asthma symptom days (AD). AD in the three studies were defined as days which included any daytime or nighttime asthma-like symptoms (cough, wheezing, nighttime awakening), unscheduled medical visits for respiratory symptoms, or use of any rescue asthma medications. AD were reported by caregivers using study-specific means including twice monthly interviews (PEAK), daily diary cards (MIST) and daily electronic home diaries (INFANT). Annualized rates of AD were determined for each participant. Risk domain of asthma severity was measured by annualized asthma exacerbations. Exacerbations were defined similarly among the studies as events involving an increase in asthma symptoms requiring treatment with systemic corticosteroids to avoid serious worsening of asthma. Study staff blinded to treatment assignment diagnosed exacerbations of asthma based on conventional criteria including symptoms not responding to SABA, frequent SABA use, prolonged moderate-severe symptoms, and physician discretion (23, 25, 26). If caregivers sought care outside of the study staff which resulted in a diagnosis of an asthma exacerbation requiring systemic steroids, the event was considered an exacerbation.

Statistical Analysis

Baseline data were summarized by study and by BMI group (Table 1, 2). The primary analyses were comparisons between NW (BMI 10–84th percentile) and OW (BMI ≥85th percentile) in asthma symptom days and exacerbations. The Chi-square and student's t test (or Wilcoxon, as appropriate) were used for comparing categorical and continuous variables between two BMI groups, respectively. Multivariable generalized linear regression under the negative binomial likelihood was used to compare main outcomes between BMI groups and study treatments with race and ethnicity as additional covariates. For analyses combining multiple studies, study was also included as a covariate. The effect of BMI status on response to ICS was determined by including an interaction between BMI group and study treatment. To demonstrate the appropriateness of collapsing all children within the BMI range 10–84th percentile and comparing NW vs. OW, we presented annualized AD and exacerbations across four BMI-percentile groups. SAS, version 9.3 (SAS Institute Inc; Cary, NC) was used. All tests were two-tailed at a level of significance of 0.05.

RESULTS

Baseline Characteristics

The baseline characteristics at randomization for 736 preschool children with asthma are shown by study and treatment in Table 1. Baseline characteristics were similar across studies, and each individual study had regional and racial/ethnic diversity. Participants

generally had mild-moderate asthma symptoms, were more likely to be male (271/736, 63%), and typically were diagnosed with asthma prior to age 2. Overweight/obese status affected 33% (244/736) of participants at baseline. A substantial portion of children were exposed to environmental tobacco smoke (291/736, 40%) and one or more pets in the home (334/736, 45%). More than half (404/736, 55%) displayed sensitization to one or more aeroallergen. On average, participants reported 1–2 asthma symptom days/week, while 64% (471/736) reported urgent care/ED use in the previous year for asthma.

Overweight/Obesity Status and Asthma Characteristics

Table 2 shows asthma characteristics at randomization for the 736 participants by overweight/obesity status. The OW group had a slightly lower prevalence of white and higher prevalence of Hispanic children. Reported home exposures to pets and tobacco smoke, and objectively measured aeroallergen sensitization were similar between BMI groups. OW children had a significantly lower percent of blood eosinophils. BMI status was not related to reported baseline symptom free days, rescue SABA use or recent urgent care. OW children had 63% higher odds of a reported hospitalization in the previous 12 months prior to enrollment (OR=1.63, 95% CI: 1.07–2.48).

Asthma Severity during Daily and Step-up ICS Treatment

In the three studies, a total of 485 children were randomized to an ICS intervention, either as daily treatment or as one of two strategies of intermittent ICS treatment. We found no evidence of OW status affecting annualized asthma symptom days while on daily ICS or either of the two intermittent ICS treatments (see Table 3; Fig 1, $p>0.05$ for Panels A-E). OW also did not affect the rate of oral steroid courses while on either of the two intermittent ICS strategies (Fig 2, $p>.05$ for panels D-E). In the combined analysis of all three studies, OW children given daily ICS did have a significantly higher rate of oral steroid bursts. As association between OW and exacerbations was noted only in the MIST study (see Table 3, Fig 2 Panel B), while in the INFANT and PEAK studies OW participants treated with daily ICS experienced similar rates of exacerbations (Fig Panel A, C).

Interaction of Overweight/Obesity Status and Treatment with Daily ICS

The PEAK trial was the only study which included both ICS-treated and placebo-treated participants in the same trial. Participants in the PEAK trial (n=269) received either daily ICS or placebo for 2 years, and are shown according to OW status (Table 4, Fig 3). Among children given placebo (n=137), OW status was associated with significantly more asthma symptoms days and oral steroid courses compared to NW status (Table 4). Placebo-treated OW children suffered 70% more symptom days (nearly 40 additional symptom days per year), and 75% more exacerbations compared to NW children. However, when similar children were randomized to daily ICS, the deleterious effects of OW status on symptoms days and oral steroid bursts were not observed. Only OW children displayed a significant ICS-related improvement in asthma symptom days ($p=0.004$) and oral steroid courses ($p=0.006$). The treatment*OW status interaction p-value approached but did not reach statistical significance for AD ($p=0.065$) or prednisone courses ($p=0.13$).

DISCUSSION

Among preschool children with a past history of asthma symptoms and not on a daily controller, OW status is associated with significantly more asthma symptom days and exacerbations. OW status at baseline was associated with greater likelihood of recent hospitalization for asthma despite similar exposure to tobacco smoke and pets in the home, and reduced blood eosinophils. However, when OW and NW children were treated with ICS (either daily, intermittent step-up or as-needed), their asthma symptom days and exacerbations were similar. The weight effect with daily ICS differed somewhat among the three studies with regard to exacerbations. OW children treated with daily ICS in the MIST trial demonstrated significantly more exacerbations compared to NW children, while this OW-effect on exacerbations while on daily ICS was not seen in the PEAK or INFANT trials. OW preschoolers in the MIST study receiving intermittent ICS did not demonstrate greater exacerbations compared similarly-treated NWs. We conclude that OW status is associated with greater impairment and risk in preschool children who are off controller therapy. However, unlike what has been reported in older children, OW status is not clearly associated with reduced treatment response to ICS. Overall, preschool children in the three trials responded well to ICS, measured by daily asthma symptoms and, to a lesser extent, exacerbations.

This is the first study to our knowledge to examine the effect of high BMI on asthma severity and ICS response in preschool aged children. Strengths of the current study include that it involved a large number of preschoolers from three highly controlled trials with documented drug adherence and extensive phenotyping. The three trials were conducted prospectively by experienced pediatric asthma centers participating in two consecutive NIH-funded research networks and recruited participants from diverse backgrounds from around the US. The three trials had similar inclusion/exclusion criteria which allowed consolidation of data (see table E1).

Monitoring of asthma severity in the preschool age is challenging, and relies mainly on clinical markers of airway disease and in most children does not incorporate measures of airway responsiveness or airway inflammation. The current recommendations for assessing asthma control in this young age group involves daily monitoring for frequency and severity of symptoms and their impact on functioning - which describes the impairment domain of asthma control. Preschool children are most impacted by episodic severe exacerbations of symptoms which often result in systemic steroid treatment and urgent care visits. The risk of asthma exacerbations corresponds to the risk domain of asthma control and is particularly important to the care of preschool children. Past studies which have attempted to evaluate the effect of high BMI in preschool children on asthma severity have been very few in number and have not utilized data from rigorously controlled trials with precise outcomes. For example, Aragona and colleagues conducted a retrospective cohort study using billing system and chart review data of hospitalized patients in the US(34). Among children <5 years of age, overweight/obese children had greater than twice the odds of a repeat emergency department visit for asthma following discharge, while overweight/obesity status exerted no effect in all other outcomes related to asthma including length of intensive care and hospital stay, total health care charges, and repeat admission. This retrospective analysis

was limited by the fact that it assessed length of stay resulting from all treatments occurring during hospitalization, and overweight/obesity effects were studied only among a subset of preschoolers (i.e. those requiring hospitalization). Silveira and colleagues(35) conducted a case control study in two Brazilian teaching hospitals involving 3–12 year olds, where cases and controls involved children with persistent asthma and intermittent asthma, respectively. The study did not stratify by age and found that obesity was associated with higher odds of persistent (versus intermittent) asthma. Both of these studies report some association between high BMI and surrogates of asthma severity, however both studies were modest in size and measurement bias and confounding from socioeconomic factors likely had some effect influence. The current study is the first to our knowledge to apply prospectively collected outcomes of both impairment and risk domains to assess the effect of body habitus on asthma severity. OW children in the current study not on daily ICS had nearly double the asthma symptom days (roughly 0.5–1.3 excess symptom days per week, or 22–63 excess symptom days per year) and more than double the average annual exacerbations compared to NW children, which equates to a difference that is clinically meaningful.

Inhaled corticosteroids are clearly efficacious versus placebo in the control and prevention of asthma symptoms for most preschool children(36–39). In fact, ICS appears to be the most efficacious single therapy for the prevention of asthma symptoms in school age children(40–43) and preschoolers(26, 44). However, poor response to ICS among preschoolers and school age children remains a problem as evidenced by the high frequency of breakthrough exacerbations in ICS-treated preschoolers and the high degree of differential response in older children (45, 46). Pooled data suggest that among preschool children the percentage of ICS responders may be as low as 40% (47, 48). Establishing markers in preschool children which predict response to ICS would be a marked advance in clinical care. Current predictors of more favorable ICS response in the PEAK trial included male sex, white race, presence of atopy and recent asthma-related ED use(49). Several studies in adults have reported that ICS is less effective in obese patients as asthma control days (22), rescue use (9), lung function (9, 50) and exacerbations (50). The mechanism(s) underlying these reduced treatment responses in the obese are unclear, but may be related to greater neutrophilic airway inflammation in OW subjects (51, 52), which has been associated with poor ICS response(53). Additionally, OW status may also cause impaired apoptotic airway cell clearance (efferocytosis), which is key to resolving inflammation and airway health (54). Based on our findings, these mechanisms do not appear to be leading in preschool children to reduced ICS efficacy.

Preschoolers in this study were treated with three possible ICS regimens (once daily, intermittent step-up, and intermittent short-term). Each analysis evaluated the effect of OW on both AD and exacerbations. Among the resulting six analyses, OW was associated with worse ICS responses in just one (MIST daily ICS on exacerbations). Among the PEAK analysis, which had the longest observation period, daily ICS significantly improved both exacerbations and AD among OW preschoolers compared to OW preschoolers treated with placebo, while a similar improvement over placebo was not seen in NW preschoolers. We conclude that overall OW preschool children display a robust response to ICS, unlike what has been reported in older OW children and adults. Though more research is needed in refining the optimal ICS strategy in this age-group (daily vs. different intermittent

approaches), the mainstay for symptomatic preschool children with asthma or recurrent wheezing at high risk for asthma has been the use of ICS which we propose should remain the case in OW preschoolers.

The current study has several limitations, including its post-hoc nature. Post-hoc analyses are important for the generation of scientific hypotheses but should be regarded cautiously until findings can be replicated. However, the hypothesis and analytic approach of the current study was proposed *a priori* (before data was released for analysis). Since the study was not specifically powered to analyze OW-related effects, it is possible that a larger analysis could demonstrate different results. We chose the most common convention for defining pediatric overweight/obesity (i.e. BMI>85th percentile), however high BMI percentile is only a marker for adiposity and can become elevated, particularly in shorter or muscular children, though this is probably less of a concern in preschool children compared to older children and adults. Since this analysis did not follow BMI-percentile over several years and did not involve a non-asthmatic comparison group, we are only able to assess phenotypic (impairment, risk) associations with OW among asthmatics. Though we did make statistical adjustments for differences between OW and NW children in race and ethnicity, we did not measure specific markers of socioeconomics (such as income or health literacy) which could be a confounding third factor associated with OW. In addition, our analysis was limited by the fact that we combined data from three studies with slightly different inclusion criteria and outcomes. We were limited to analyzing outcomes which were measured similarly (asthma symptom days, exacerbations) in all three studies and we did not analyze lung function. We chose to analyze only the children who were 12–59 months of age at enrollment to account for the slightly different ages across studies. Lastly, we did not attempt to adjust for possible variations in adherence.

In conclusion, early life high BMI does appear to worsen both impairment and risk domains of asthma severity in preschool children off controller therapy. Interventions which reduce early life weight gain and overweight/obesity status may benefit respiratory health in preschool children and deserves future study of interventions aimed at reducing adiposity. OW status was not clearly associated with reduced response to ICS. Overall, preschool children in the three trials responded well to ICS, measured by daily asthma symptoms and, to a lesser extent, exacerbations, and thus ICS should remain the first-line treatment option for this high morbidity group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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INFANT https://ClinicalTrials.gov number,

PEAK https://ClinicalTrials.gov number,

MIST https://ClinicalTrials.gov number,

Abbreviations

ANOVA	analysis of variance
AD	asthma symptom days
BMI	body mass index
CAMP	Childhood Asthma Management Program
CARE	Childhood Asthma Research and Education Program
CDC	Centers for Disease Control & Prevention
CI	confidence intervals
ED	emergency department
ICS	inhaled corticosteroids
INFANT	Individualized Therapy for Asthma in Toddlers
LTRA	leukotriene receptor antagonist
MIST	Maintenance versus Intermittent Inhaled Steroids in Wheezing Toddlers trial
OR	odds ratio
OW	overweight/obese
PEAK	Prevention of Early Asthma in Kids trial
SABA	short-acting Beta-2-agonists

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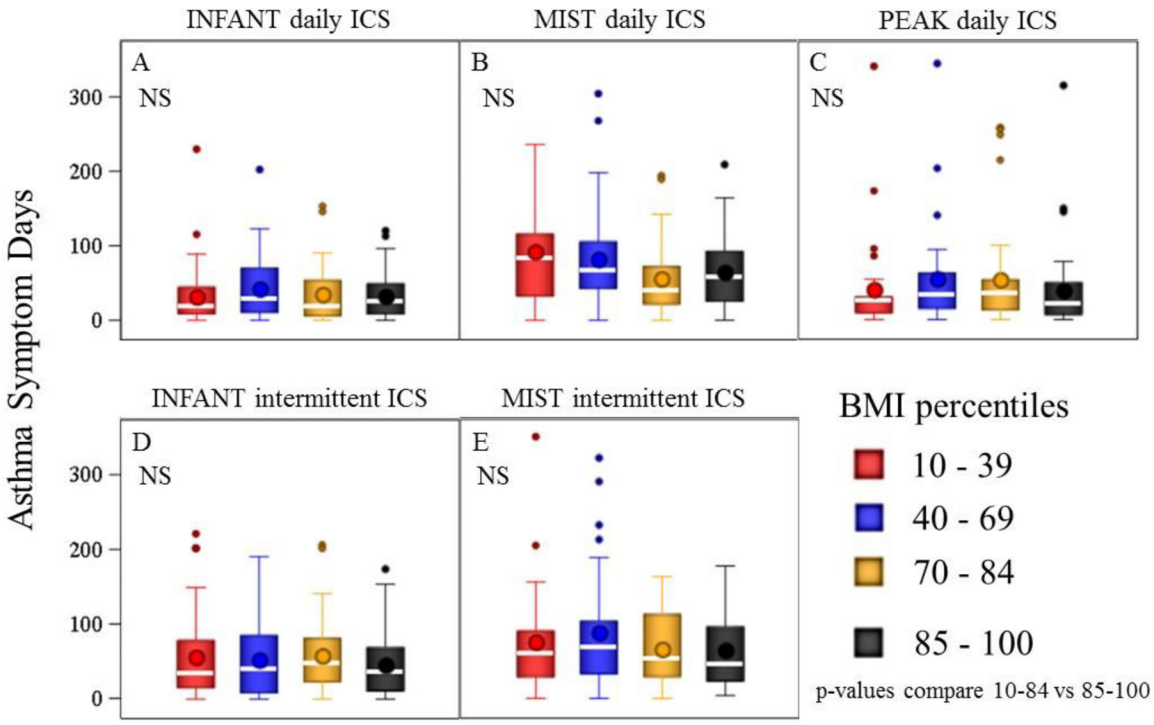

Figure 1.

Annualized Asthma Symptom Days among four BMI-percentile groups. Each panel indicates the study and treatment. Box plots represent medians and intra-quartile ranges. Whiskers represent 95th percentile ranges and points denote outliers. BMI-percentile grouping did not affect asthma symptom days, p-values were non-significant (NS) for all panels A-E comparing BMI-percentiles 10–84 vs. 85–100.

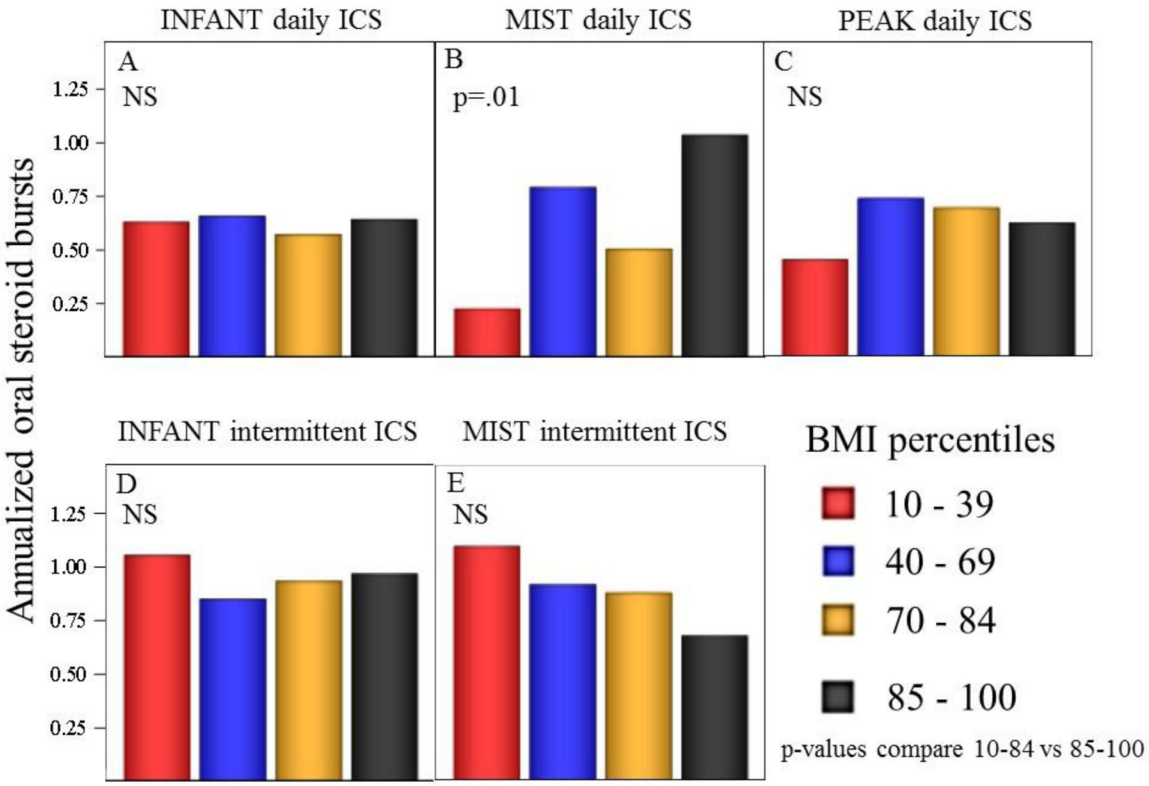

Figure 2.

Annualized exacerbations requiring oral steroid bursts among four BMI-percentile groups. Each panel indicates the study and treatment. Box plots represent medians and interquartile ranges. Whiskers represent 95th percentile ranges and points denote outliers. BMI-percentile grouping did not affect asthma exacerbations with the exception of MIST daily ICS. P-values were non-significant (NS) in panels (A, C, D, E) comparing BMI-percentile groups 10–84 vs. 85–100.

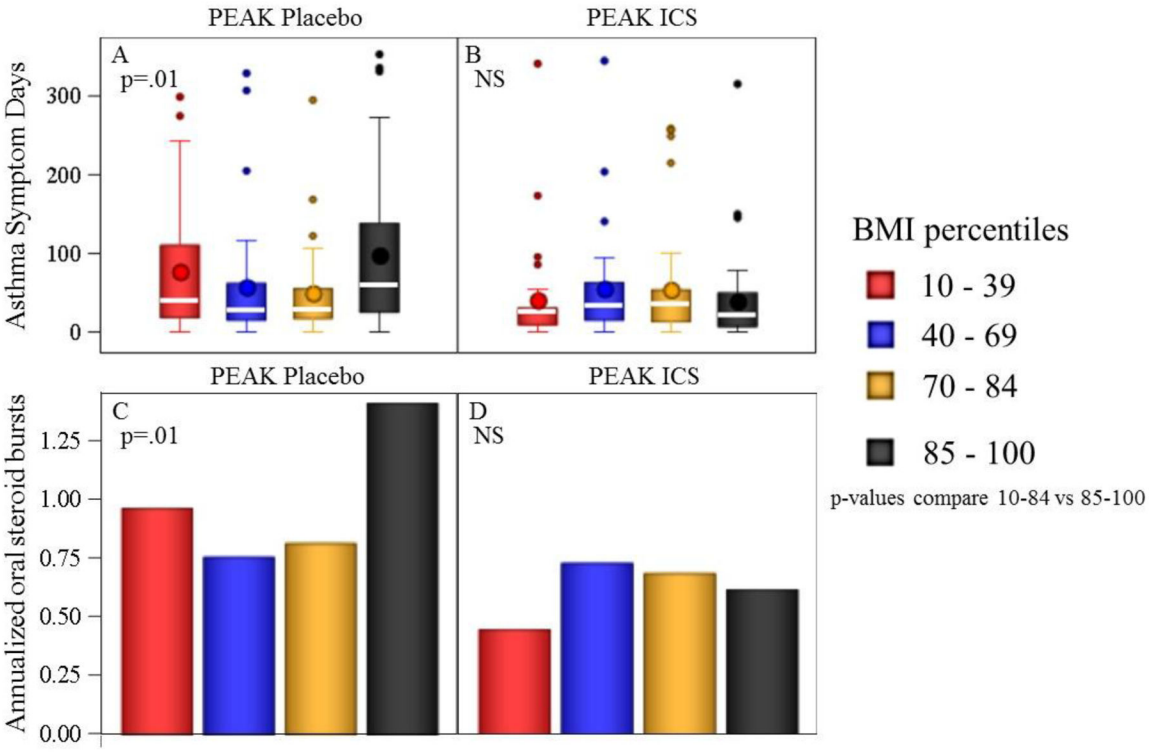

Figure 3.

Exacerbations and asthma symptom days among four BMI-percentile groups. Box plots (a, b) represent medians and intra-quartile ranges. Whiskers represent 95th% ranges. BMI-percentile grouping did not affect AD or exacerbations among ICS-treated, p>0.05; OW participants treated with placebo demonstrated significantly greater AD and exacerbations compared to NW (p=0.01 for both comparison). P-values in all panels compare BMI-percentiles 10–84 vs. 85–100.

Table 1.

Baseline characteristics of participants by clinical trial

	PEAK Placebo (N=137)	MIST intermittent short-term ICS (N=104)	INFANT intermittent as-needed ICS / Daily ICS (N=245)*	PEAK daily ICS (N=132)	MIST daily ICS (N=118)
Age at enrollment (months)†	35.9 (6.9)	37.9 (8.2)	43.6 (10.5)	36.0 (7.1)	38.3 (9.2)
Age at diagnosis (months)	15.6 (10.0)	19.6 (10.4)	22.1 (12.8)	18.0 (10.4)	17.9 (9.9)
Female, n (%)	51 (37.2)	27 (26)	101 (41.2)	51 (38.6)	41 (34.7)
Race/Ethnicity, n (%)					
Non-Hispanic White	73 (53.3)	48 (46.2)	77 (31.4)	73 (55.3)	41 (34.7)
Non-Hispanic Black	20 (14.6)	13 (12.5)	73 (29.8)	13 (9.8)	21 (17.8)
Hispanic	25 (18.2)	31 (29.8)	64 (26.1)	28 (21.2)	41 (34.7)
Other Race	19 (13.9)	12 (11.5)	31 (12.7)	18 (13.6)	15 (12.7)
Weight (kg)	15.2 (2.1)	15.9 (2.8)	17.3 (3.7)	15.3 (2.6)	16.1 (2.9)
BMI percentile	66.3 (25.6)	65.0 (25.0)	67.8 (25.0)	66.6 (25.9)	71.8 (20.9)
BMI ≥ 85 percentile, n (%)	44 (32.1)	33 (31.7)	89 (36.3)	40 (30.3)	38 (32.2)
Tobacco smoke exposure, n (%)	54 (39.4)	37 (36.3)	96 (39.2)	52 (39.4)	52 (44.1)
Pets in home, n (%)	60 (43.8)	45 (43.3)	113 (46.1)	63 (47.7)	53 (44.9)
Positive aeroallergen test, n (%)	79 (57.7)	62 (60.2)	110 (46.6)	82 (62.1)	71 (60.2)
Ever have eczema, n (%)	66 (48.2)	53 (51)	156 (63.7)	74 (56.1)	59 (50)
IgE (kU/L) **	40.4 (12.1, 111.0)	58.0 (21.6, 242.0)	85.5 (27.0, 244.5)	43.0 (15.0, 117.0)	59.7 (25.0, 179.0)
Blood eosinophils (%) **	3.0 (1.6, 5.0)	4.0 (2.0, 5.7)	3.5 (2.0, 6.0)	3.8 (2.0, 6.0)	3.0 (2.0, 6.2)
Average SFDs per week	5.1 (1.7)	4.7 (2.2)	6.1 (1.2)	5.1 (1.6)	4.7 (2.1)
Average SABA puffs per week **	0.6 (0.0, 1.5)	0.0 (0.0, 1.0)	0.0 (0.0, 2.2)	0.5 (0.0, 1.4)	0.0 (0.0, 1.0)
Urgent/ED visit in the past year, n (%)	64 (46.7)	61 (58.7)	214 (87.3)	62 (47)	70 (59.3)
Hospitalized in the past year, n (%)	10 (7.3)	18 (17.3)	48 (19.6)	10 (7.6)	19 (16.1)

Values represent means (SD) unless noted.

* - represents same participants as INFANT daily ICS due to crossover design.

† - inclusion age ranges varied slightly in the three studies. Analysis included only children 24–59 months at enrollment.

** - denotes median and interquartile ranges. ICS – inhaled corticosteroid. BMI – body mass index. SFD – symptoms free days. SABA – short acting beta-agonist. PEAK – Prevention of Early Asthma in Kids trial, MIST - Maintenance versus Intermittent Inhaled Steroids in Wheezing Toddlers trial, INFANT - Individualized Therapy for Asthma in Toddlers

Table 2.

Baseline asthma-related characteristics by BMI status

	BMI-percentile		
	10–84th (N=492)	**≥ 85th (N=244)**	**p-value**
Age at enrollment in months, mean (SD)	38.9 (9.1)	39.6 (9.9)	0.45
Age at diagnosis in months, mean (SD)	19.4 (11.4)	18.4 (11.2)	0.31
Weight in kg, mean (SD)	15.0 (2.1)	18.4 (3.7)	<0.0001
Female	193 (39.2%)	78 (32%)	0.055
Race			
Non-Hispanic White	**223 (45.3)**	**89 (36.5)**	**0.0223**
Non-Hispanic Black	95 (19.3)	45 (18.4)	0.78
Hispanic	**108 (22.0)**	**81 (33.2)**	**0.0010**
Other Race	66 (13.4)	29 (11.9)	0.56
Tobacco smoke exposure	188 (38.3)	103 (42.4)	0.16
Pets in Home	225 (45.7)	109 (44.7)	0.79
Positive Aeroallergen Test	278 (57.3)	126 (52.3)	0.20
Child ever have eczema	279 (56.7)	129 (52.9)	0.98
IgE (kU/L) *	64.5 (21.6, 202.0)	49.0 (16.1, 161.5)	0.060
Blood eosinophils % *	**3.7 (2.0, 6.1)**	**3.0 (1.9, 5.0)**	**0.0068**
Average SFDs per week, mean (SD)	5.3 (1.8)	5.3 (1.8)	0.62
Average SABA puffs per week *	0.4 (0.0, 1.4)	0.0 (0.0, 1.3)	0.095
Urgent/ED visit in the past year	310 (63)	161 (66)	0.43
Hospitalized in the past year	**60 (12.2)**	**45 (18.4)**	**0.0226**

Values represent counts (%) unless noted. BMI – body mass index, SFD – symptom free days, SABA – short-acting beta-agonist, ED – emergency department.

* - Wilcoxon test

Table 3.

Asthma severity during daily or step-up inhaled corticosteroid (ICS) intervention by BMI-status

	BMI-percentile		
Daily ICS*	**10–84th (N=328)**	**≥85th (N=157)**	**p-value**
Asthma Symptom Days, mean (95% CI)[1]	47.2 (40.8, 54.7)	43.0 (35.1, 52.6)	0.44[3]
Prednisone bursts, mean (95% CI)[2]	0.6 (0.5, 0.8)	0.8 (0.6, 1.1)	0.10[3]
Intermittent short-term ICS**			
N	71	33	
Total intervention days, median (IQR)	359 (350, 367)	362 (343, 369)	
Asthma Symptom Days, mean (95% CI)[1]	61.8 (48.1, 79.3)	52.9 (36.9, 76.0)	0.46[4]
Prednisone bursts, mean (95% CI)[2]	1.1 (0.8, 1.6)	0.8 (0.5, 1.3)	0.25[4]
Intermittent as needed ICS***			
N	140	75	
Total intervention days, median (IQR)	113 (111, 117)	113 (112, 118)	
Asthma Symptom Days, mean (95% CI)[1]	53.3 (42.1, 67.4)	47.3 (35.0, 63.9)	0.53[4]
Prednisone bursts, mean (95% CI)[2]	1.0 (0.7, 1.4)	1.1 (0.7, 1.7)	0.72[4]

BMI – body mass index, SFD – symptom free days.

* - data combined from INFANT, PEAK and MIST trials,

** - data from MIST trial,

*** - data from INFANT trial.

1 – annualized symptom days.

2 – bursts represent new oral steroid starts.

3 – p-values adjusted for trial and race/ethnicity

4 – p-values adjusted for race/ethnicity

Table 4.

Response to inhaled corticosteroids (ICS) by BMI-status (PEAK study only)

	BMI-percentile		
Placebo-treated	**10–84th (N=93)**	**≥85th (N=44)**	**p-value**[3]
Total intervention days, median (IQR)	672 (661, 679)	672 (667, 685)	
Asthma Symptom Days, mean (95% CI)[1]	53.2 (40.1, 70.5)	90.7 (61.8, 133.2)	0.021
Exacerbations, mean (95% CI)[2]	0.8 (0.6, 1.1)	1.4 (1.0, 2.1)	0.009
Daily ICS			
N	92	40	
Total intervention days, median (IQR)	672 (663, 679)	672 (669, 679)	
Asthma Symptom Days, mean (95% CI)[1]	44.9 (34.3, 58.8)	41.2 (27.6, 61.5)	0.72
Exacerbations, mean (95% CI)	0.6 (0.4, 0.8)	0.6 (0.4, 1.0)	0.78
p-value comparing ASD (Placebo vs ICS)	0.37	0.004	
p-value comparing exacerbations (Placebo vs ICS)	0.20	0.006	
OW status *Treatment interaction on symptom days			0.065
OW status *Treatment interaction on exacerbations			0.13

BMI – body mass index,

1 – annualized symptom rate.

2 – bursts represent new oral steroid starts.

3 – p-values adjusted for race/ethnicity, PEAK – Prevention of Early Asthma in Kids trial