USAsthma SUMMIT 2024

Obesity-Related Asthma in Children and Adolescents

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Children’s Hospital Colorado and the
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Children's Hospital Colorado
Here, it's different.

Affiliated with
University of Colorado
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Disclosures

- Advisory Board Member:
  - Sanofi
  - Regeneron
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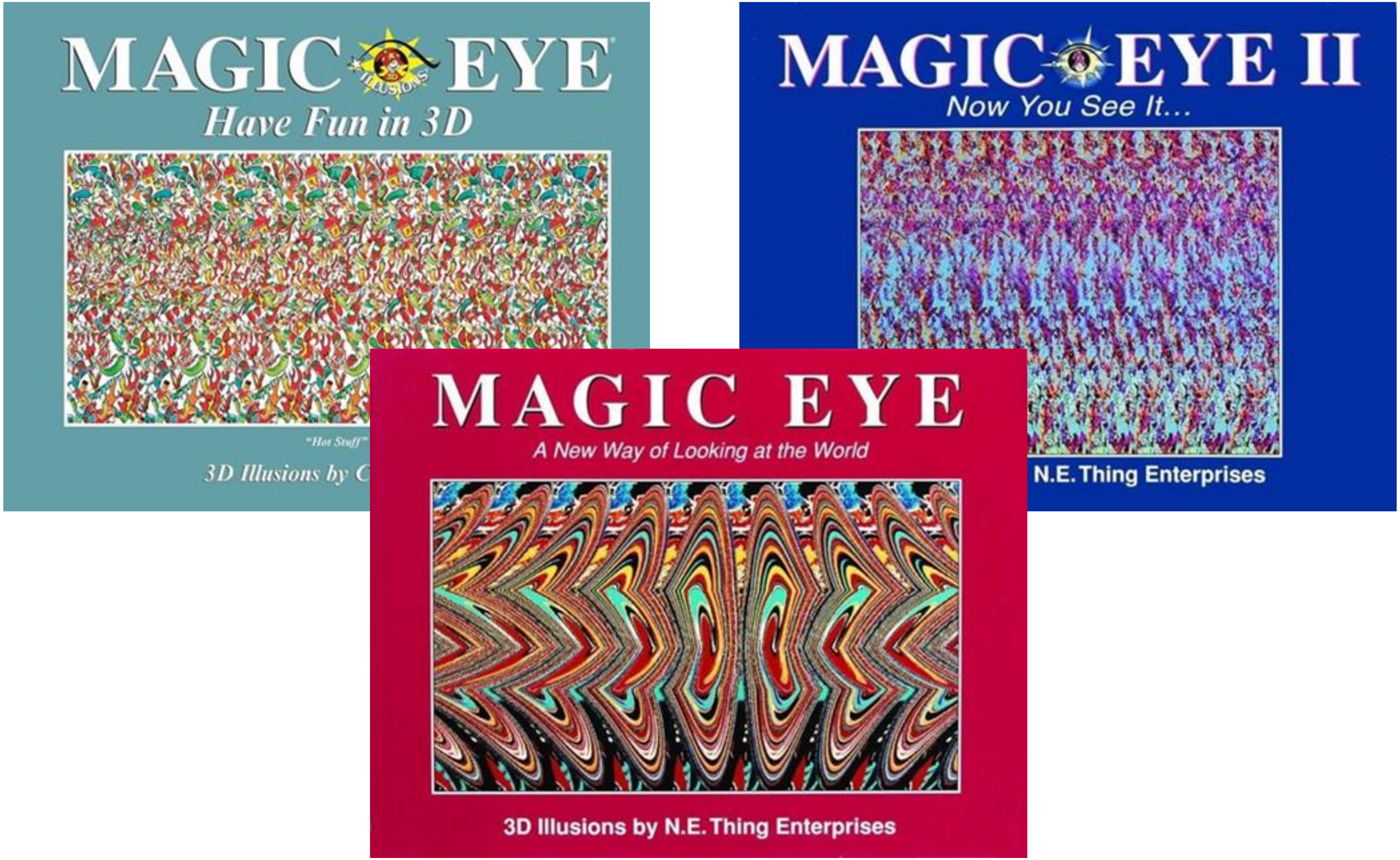
Objectives

1. Recognize the symptomatic and causative interplay between asthma and obesity in children
2. Identify the unique pathophysiology of the obesity-related asthma phenotype
3. Develop a strategy to treat pediatric patients with asthma and obesity
4. Explore the potential role of novel obesity therapies to improve asthma control

What is an Autostereogram?


MAGIC EYE
Have Fun in 3D
"Hot Stuff"
3D Illusions by C
MAGIC EYE II
Now You See It...
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A New Way of Looking at the World
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Increased Asthma Burden in Obese Patients

Symptoms

- Longer duration of cough
- Increased sputum production
- Increased nocturnal symptoms
- Increased dyspnea
- Lower quality of life

Health Care Utilization

- More frequent exacerbations
- Higher risk of mechanical ventilation
- Longer lengths of stay

Table 2. Oral steroid prescription overall ($N = 16\,763$).

	Rate ratio	95% CI
Obesity status		
Never overweight/obese	ref	
Sometimes overweight/obese	1.11	1.03-1.20
Always overweight/obese	1.14	1.06-1.22

Averill SH, et al. Ann Allergy Asthma Immunol 2024;132:30-9.
Lucas JA, et al. J Asthma 2020;57:1288-97.
Peters U, et al. J Allergy Clin Immunol 2018;141:1169-79.

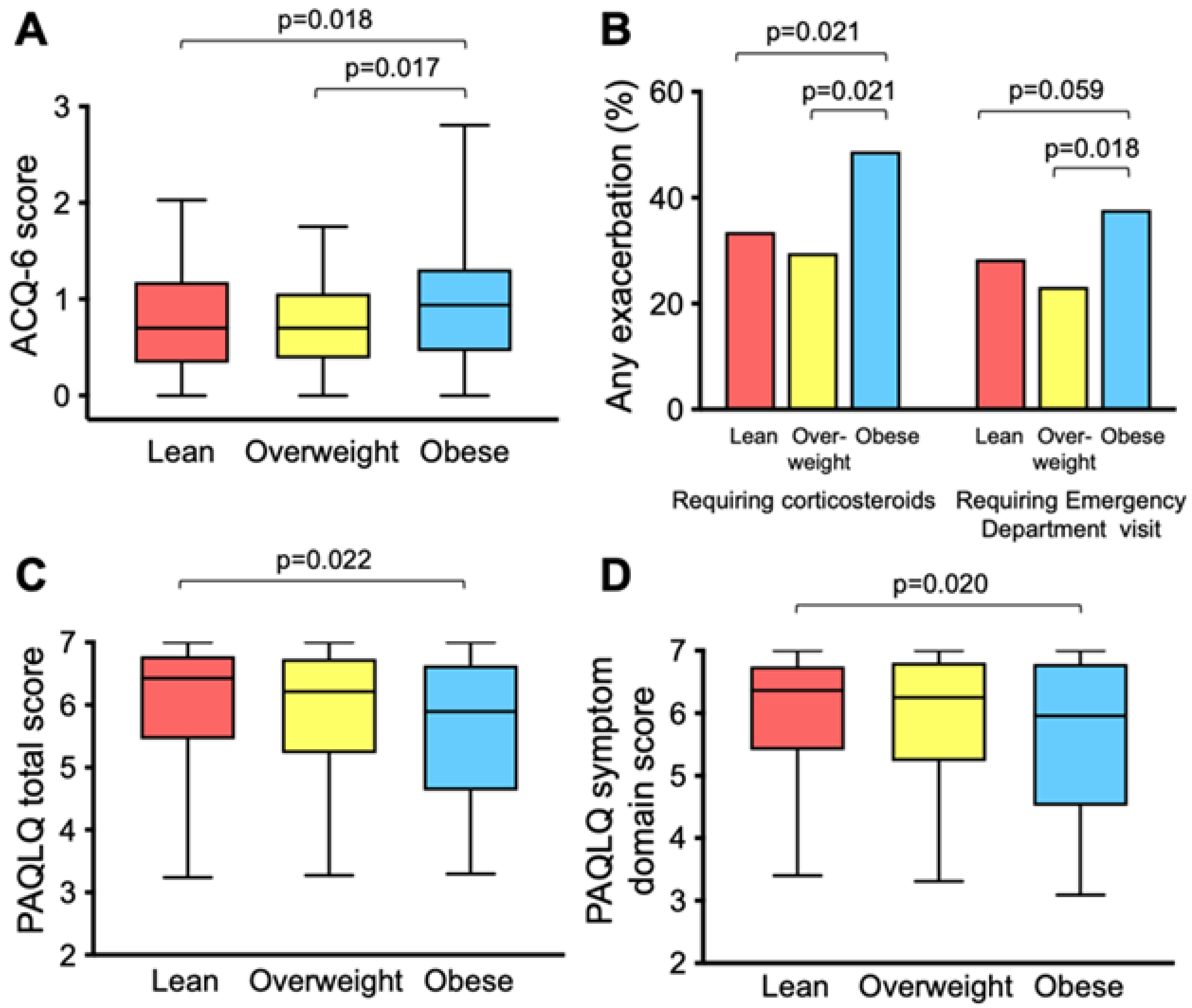


FIGURE 2. (**A**) Asthma Control Questionnaire (ACQ) 6-item scores, (**B**) exacerbation occurrence, and (**C**) Pediatric Asthma Quality of Life Questionnaire (PAQLQ) total scores and (**D**) PAQLQ symptom domain scores in lean (red), overweight (yellow), and obese (blue) children at 12 months. Boxplot whiskers depict the 5th and 95th percentiles.

Fitzpatrick AM, et al. J Allergy Clin Immunol Pract 2022;10:815-26.

TABLE 2 Overall and subgroup analyses of overweight or obesity with the risk of having asthma and wheeze

Groups	Number of Included Studies for Asthma/Wheeze	Asthma		Wheeze	
		OR (95% CI); *P*	I^2	OR (95% CI); *P*	I^2
Overall analysis					
Overweight or obesity	55/11	1.30 (1.23-1.39); <0.001	84.6%	1.90 (1.38-2.63); <0.001	67.2%
Subgroup analysis for overweight or obesity					
By gender					
Both genders	18/6	1.33 (1.20-1.46); <0.001	88.0%	1.78 (1.24-2.55); 0.002	69.2%
Boys	19/2	1.27 (1.15-1.40); <0.001	72.4%	1.84 (0.51-6.66); 0.356	77.7%
Girls	19/3	1.34 (1.16-1.56); <0.001	87.2%	3.00 (0.83-10.80); 0.092	78.7%
By comparison					
Overweight	33/4	1.22 (1.14-1.31); <0.001	75.2%	3.05 (1.33-6.97); 0.008	80.6%
Obesity	20/2	1.40 (1.29-1.52); <0.001	78.2%	1.72 (1.32-2.25); <0.001	0.0%
Overweight or obesity	3/5	2.12 (0.77-5.84); 0.144	72.8%	1.55 (0.89-2.70); 0.121	62.3%

Deng X, et al. Pediatric Obesity 2019;14:e12532.

Asthma Impacts Obesity Development

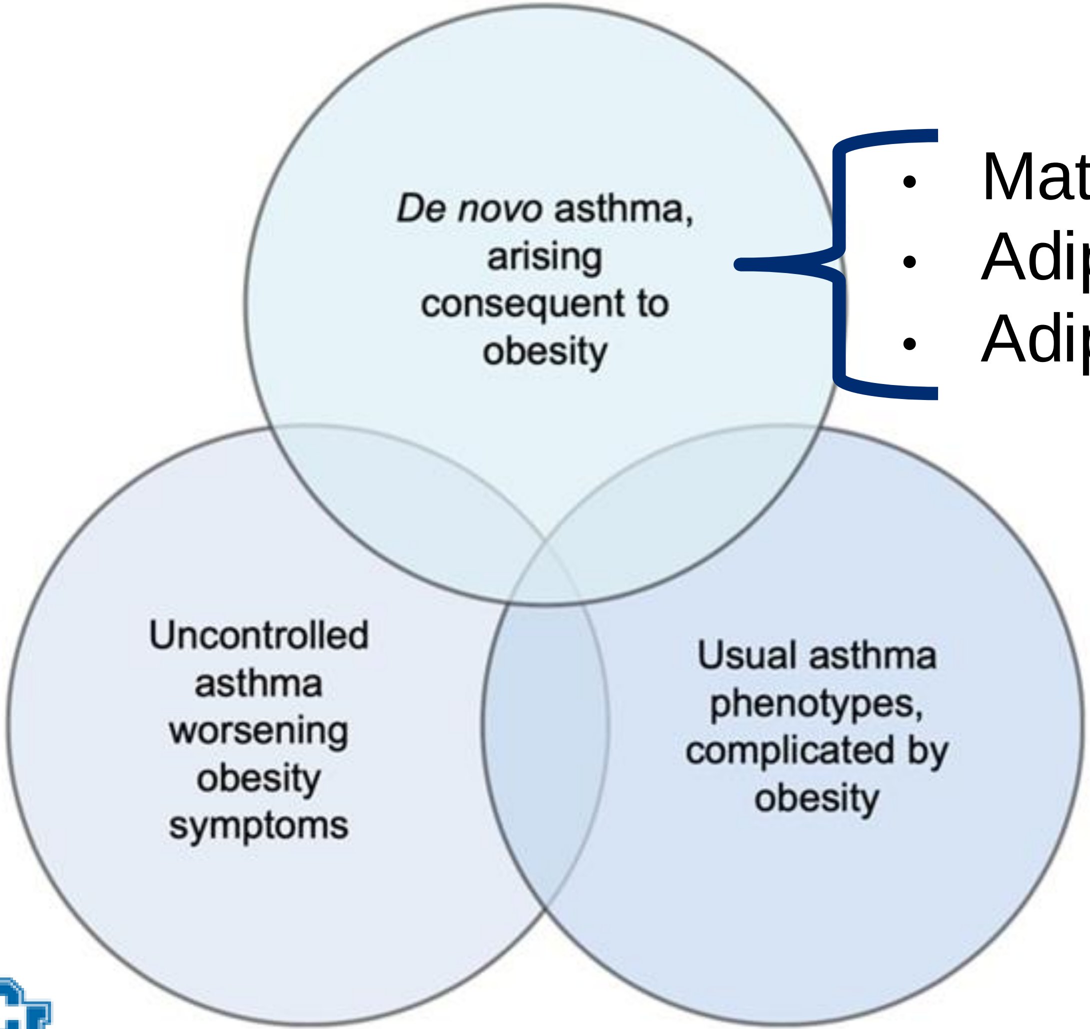
- Exercise-induced symptoms Decreased physical activity
- Asthma exacerbations frequent systemic steroids

Obesity

- Obesity development in children with asthma was reduced with increased controller medication use

Reyes-Angel J, et al. Lancet Child Adolesc Health 2022;6:713-24.

Obesity Impacts Asthma Development



- Maternal obesity □ Asthma in offspring
- Adiposity <6 y □ Childhood-onset asthma
- Adiposity pre-puberty □ Young adult asthma

Peters U, et al. J Allergy Clin Immunol 2018;141:1169-79.
Reyes-Angel J, et al. Lancet Child Adolesc Health 2022;6:713-24.

Obesity Affects Asthma Severity

- Genetic predisposition
- Mechanical and physiologic lung/airway changes
- Altered systemic and airway immunobiology
- Airway and systemic inflammation
- Metabolic dysregulation
- Altered microbiome
- Increased susceptibility to environmental factors

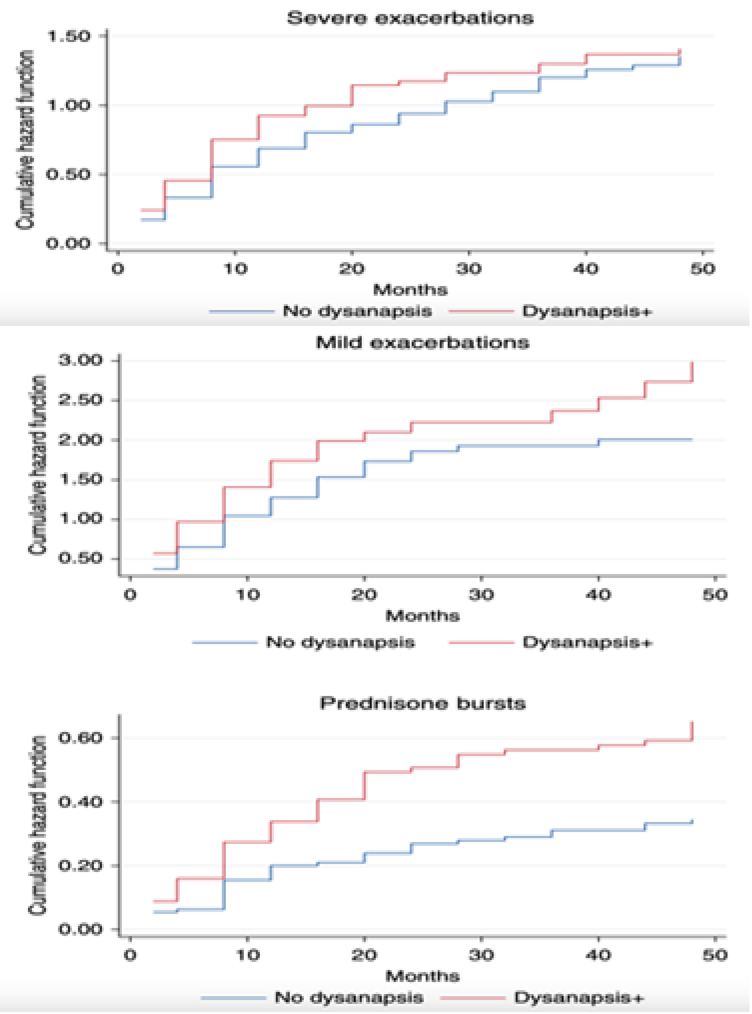
Airway Mechanics in Obesity

Childhood	Adulthood
Obstructive Pattern	**Restrictive Pattern**
Normal FEV1	Low FEV1
Normal FVC	Low FVC
Low FEV1/FVC	Normal FEV1/FVC

Excess chest wall weight + increased abdominal fat ▯
reduce diaphragmatic excursion and thoracic expansion▯
decreased respiratory compliance ▯
increased work of breathing

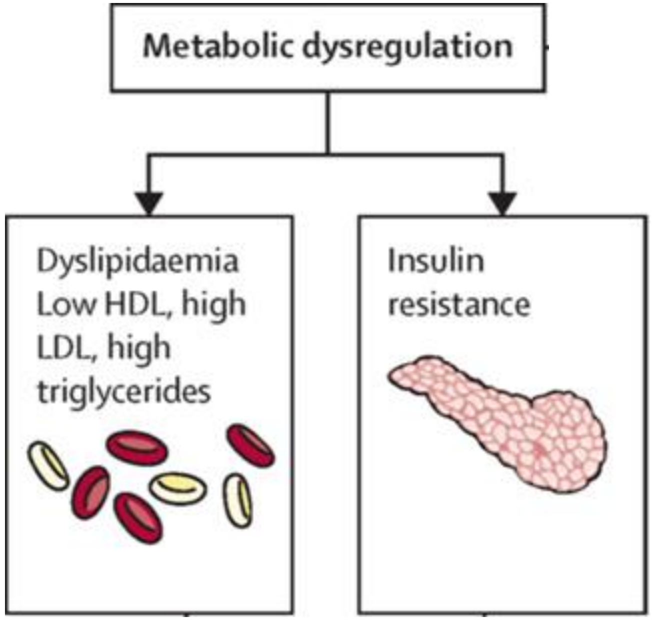
Airway Dysanapsis

- Asymmetrical growth of lung parenchyma and airway caliber
  - Supra/Normal FEV1 and FVC
  - Larger effects on FVC ⍰ low FEV1/FVC ratio
- Driven by central obesity
- Developmental effect and not just mechanical impact on lung function



Forno E, et al. Am J Respir Crit Care Med 2017;195:314-23.

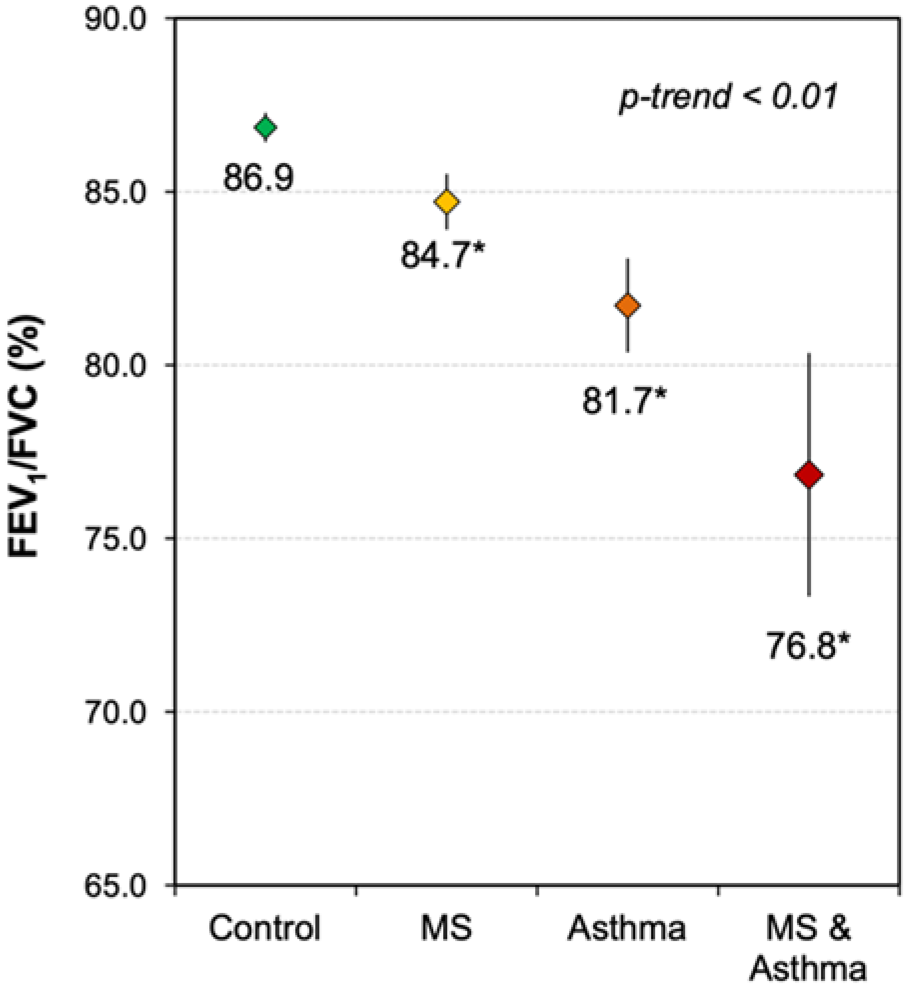
Metabolic Dysregulation



- Higher blood insulin levels in early childhood are associated with increased risk of asthma through adolescence and adulthood, independent of BMI
- Insulin resistance alters airway smooth muscle
  - Increased proliferation
  - Pro-contractile phenotype
- Insulin resistance and low HDL promotes TH1 inflammation

Peters U, et al. J Allergy Clin Immunol 2018;141:1169-79.
Reyes-Angel J, et al. Lancet Child Adolesc Health 2022;6:713-24.

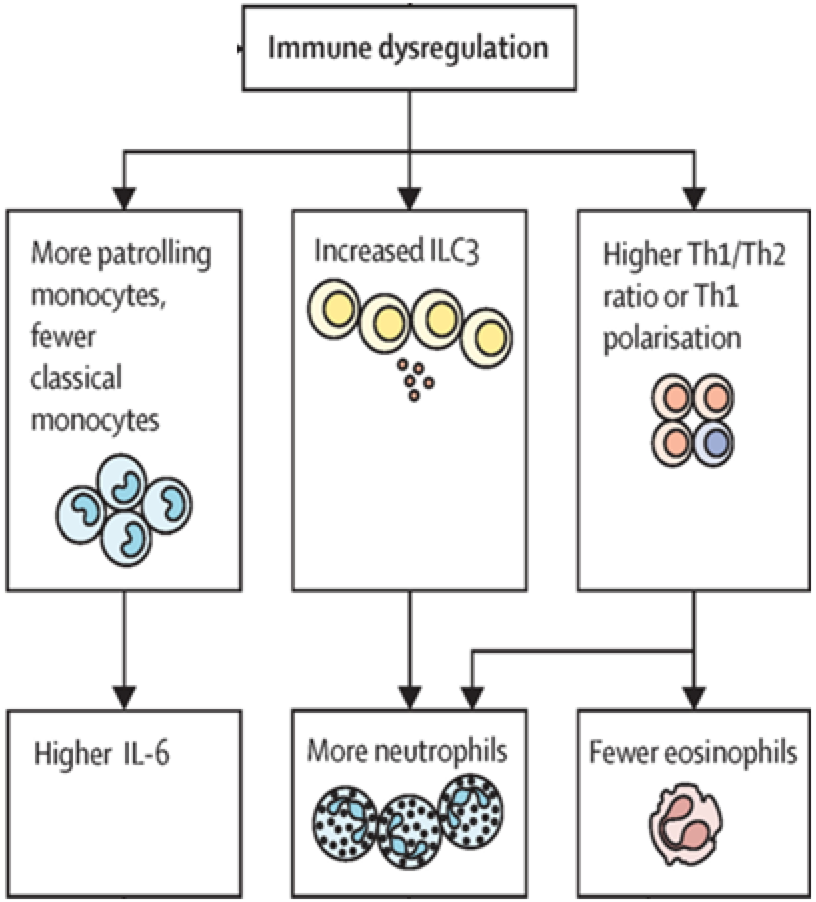
Metabolic Dysregulation & Lung Function



- Insulin resistance has been associated with lower FEV1/FVC
- Higher leptin levels in obese adolescents correlate inversely with FEV1, FVC, and FEV1/FVC

Peters U, et al. J Allergy Clin Immunol 2018;141:1169-79.
Reyes-Angel J, et al. Lancet Child Adolesc Health 2022;6:713-24.

Immune Dysregulation



- Monocytes in adipose tissue □ relative hypoxia □ activation □ IL-6 and TH1 inflammation
- ILC3 □ increased and produce IL17A □ neutrophils
- ILC2 □ increased survival mediated by leptin □ augments allergic response

Peters U, et al. J Allergy Clin Immunol 2018;141:1169-79.
Reyes-Angel J, et al. Lancet Child Adolesc Health 2022;6:713-24.

IL-6, TH1 Phenotype, and Control

TABLE I. Associations between plasma IL-6, asthma outcome measures, and baseline markers of inflammation

Cross-sectional*	Low IL-6 (n = 39)	Med-Low IL-6 (n = 39)	Med-High IL-6 (n = 39)	High IL-6 (n = 38)	*P* value†
Clinical outcome measures					
BMI Percentile, mean ± SD	63.2 ± 27.4	79.3 ± 20.8‡	84.8 ± 19.3‡	78.1 ± 30.8‡	<.001

TABLE II. Associations between plasma IL-6 and asthma outcome measures during 3-y longitudinal follow-up (three 1-y measurements after baseline, n = 8 subjects missing follow-up data)

Longitudinal	Low IL-6 (n = 37)	Med-High IL-6* (n = 110)	Effect size (95% CI)	*P* value†
Clinical outcome measures				
Asthma exacerbation rate per year, mean ± SD‡	0.40 ± 0.87	0.97 ± 1.90	IRR = 2.09 (1.02 to 4.28)	.04
1-y follow-up	0.33 ± 0.79	1.19 ± 2.40		
2-y follow-up	0.53 ± 1.11	0.91 ± 1.64		
3-y follow-up	0.33 ± 0.66	0.75 ± 1.33		
Proportion of participants with ER visit for asthma per year, % (n)	12 (12)	27 (79)	OR = 3.41 (0.88 to 13.1)	.08
1-y follow-up	17 (6)	33 (36)		
2-y follow-up	12 (4)	26 (26)		
3-y follow-up	7 (2)	21 (17)		
Spirometry outcome measures				
FEV_1 (% predicted), mean ± SD	93.1 ± 9.6	88.3 ± 16.2	$\beta = -5.8$ (−11.2 to −0.5)	.03
1-y follow-up	93.2 (10.2)	88.6 (15.5)		
2-y follow-up	95.1 (9.6)	87.4 (16.8)		
3-y follow-up	91.0 (8.9)	88.9 (16.5)		
FVC (% predicted), mean ± SD	104.8 ± 11.3	101.4 ± 15.2	$\beta = -6.4$ (−11.6 to −1.16)	.01
1-y follow-up	105.0 ± 11.2	101.3 ± 14.3		
2-y follow-up	105.2 ± 11.4	101.1 ± 15.3		
3-y follow-up	104.0 ± 11.5	101.9 ± 16.2		

Permaul P, et al. J Allergy Clin Immunol Pract 2021;9:2916-9.

Environmental Exposures	
Smoking	• Maternal smoking a risk factor for both asthma and obesity.
Air Pollution	• Exposure to air-pollution a risk factor for both asthma and obesity.

Genetic Factors	
CHI3L1	• Involved in fat accumulation and Th2 inflammation.
PRKCA	• Candidate gene associated with BMI and asthma.
LEP	• Associated with asthma and with obesity pathogenesis.
DENND1B	• Largest GWAS of BMI and asthma in children & adults.

Diet

Diet	
Fructose	• High fructose diet promotes systemic metabolic dysfunction, increases AHR and airway oxidative stress.
Vitamin D	• Obesity is associated with low vitamin D – may be a risk factor for both obesity and asthma.
High-fat diet	• Increase in lung innate lymphoid cells and IL-1β pathway – increases innate and allergic airway AHR, and neutrophilic airway inflammation.

SCFAs

High Fiber

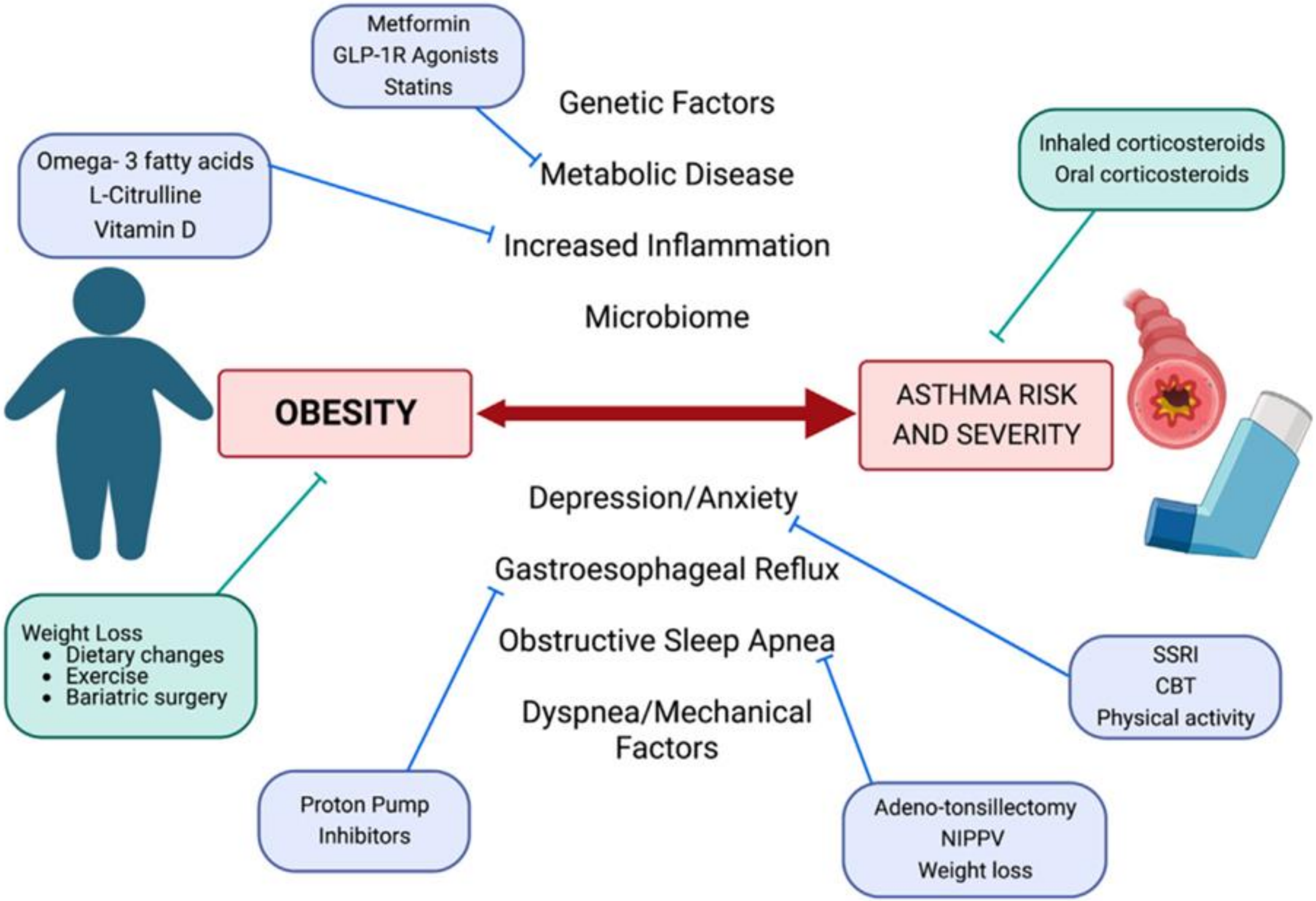
Low fiber d

Antibiotics

Probiotics	• Probiotic supplementation in early life reduces risk of atopy.
Airway microbiome	• Increased BMI associated with changes in airway microbiome and decreased eosinophilia

Mechanical Effects	
Lung function	• Changes in the mechanical properties of the lungs and chest wall lead to significant decrements in FRC and ERV.

Peters U, et al. J Allergy Clin Immunol 2018;141:1169-79.



Averill SH, et al. Ann Allergy Asthma Immunol 2024;132:30-9.

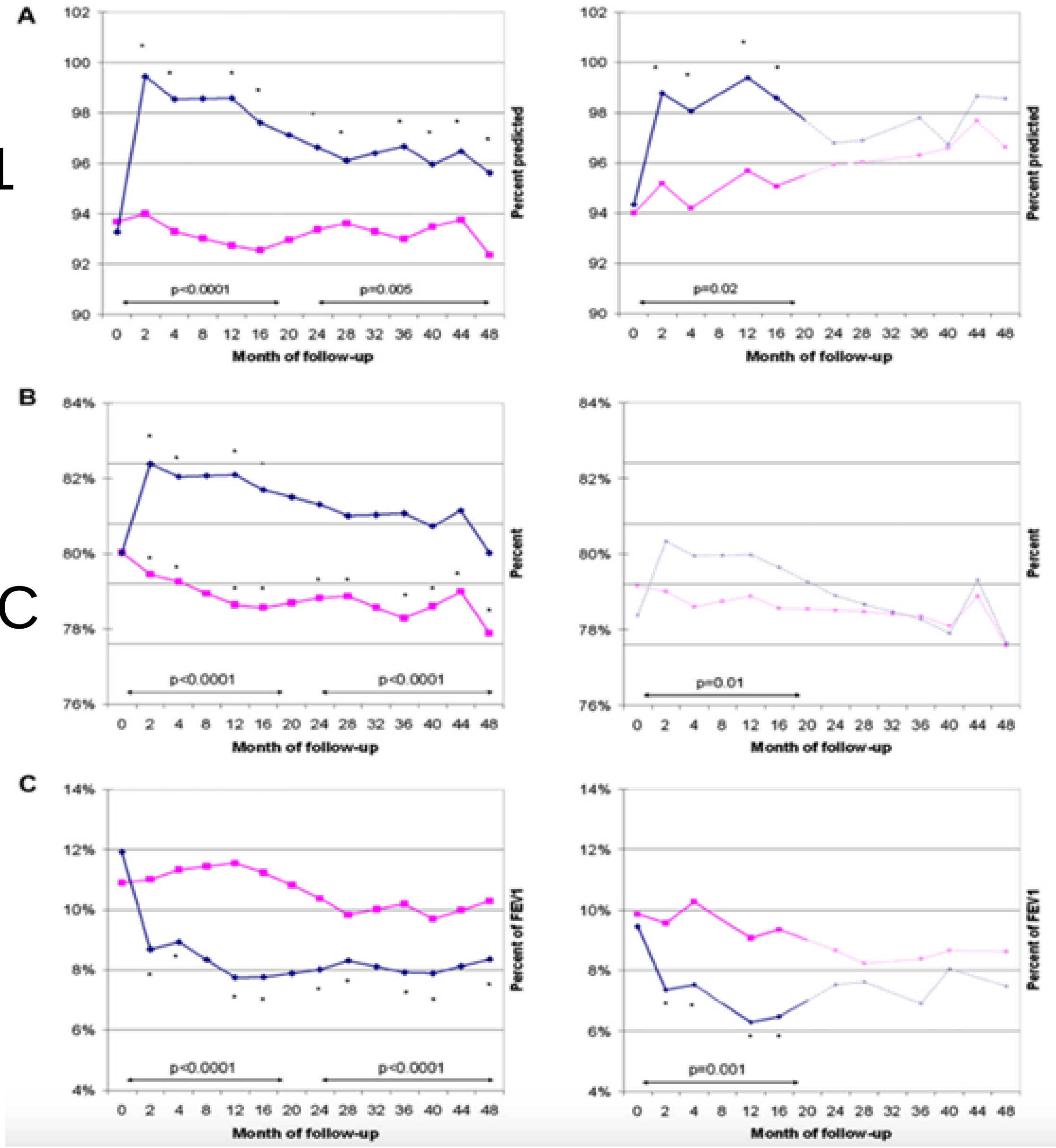
Reduced Response to ICS in Children with Obesity

Non-Obese | Obese

Pre-FEV1

Pre-FEV1/FVC

BDR

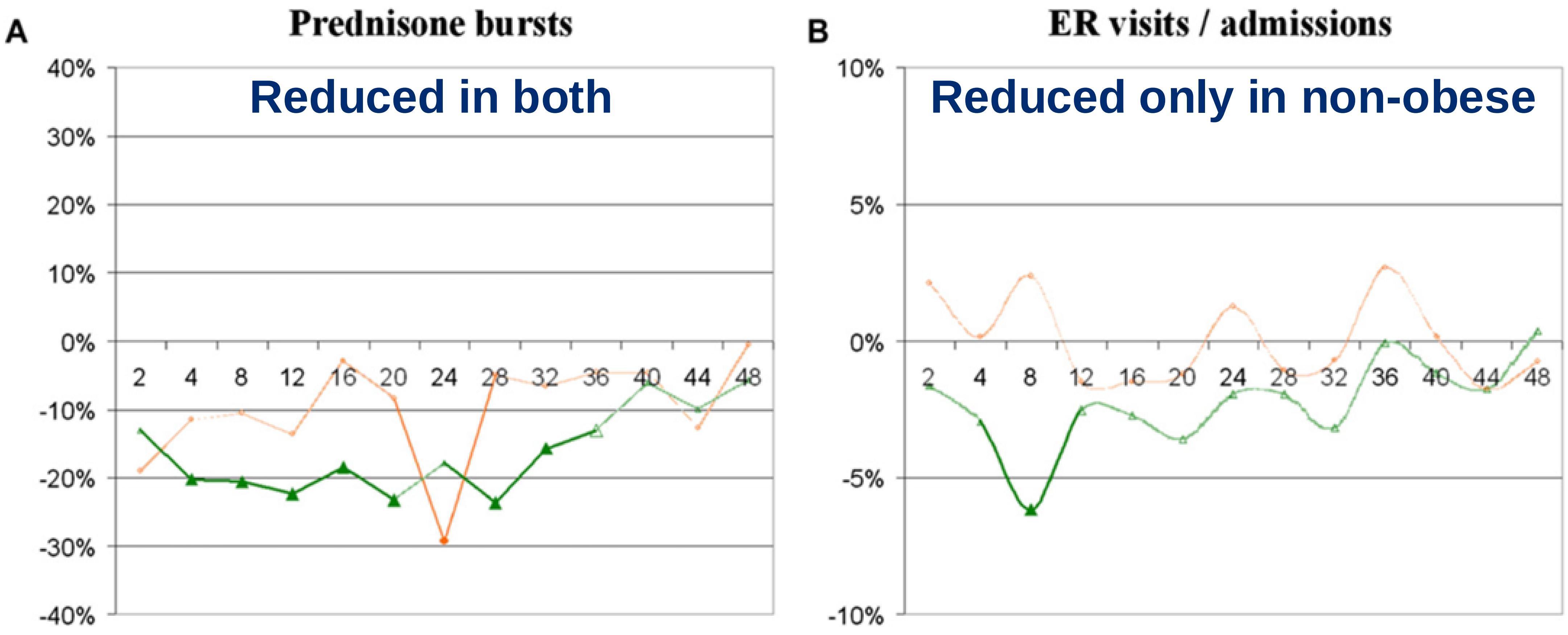


Budesonide

Placebo

Forno E, et al. J Allergy Clin Immunol 2011;127:741-9.

ICS Treatment Responses (cont)

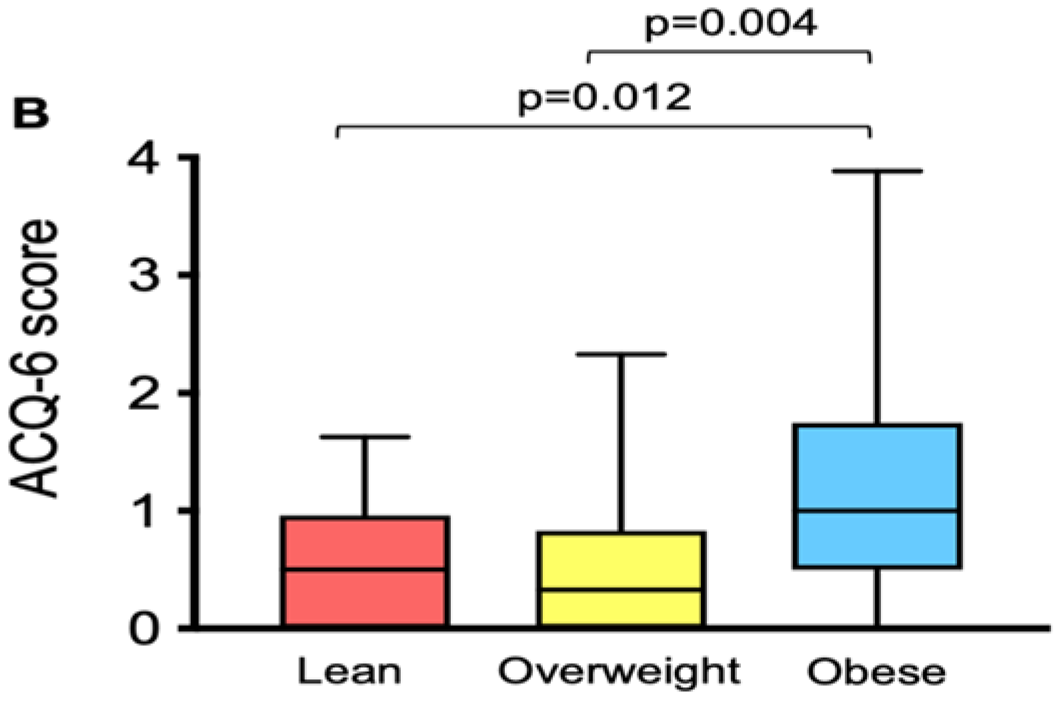


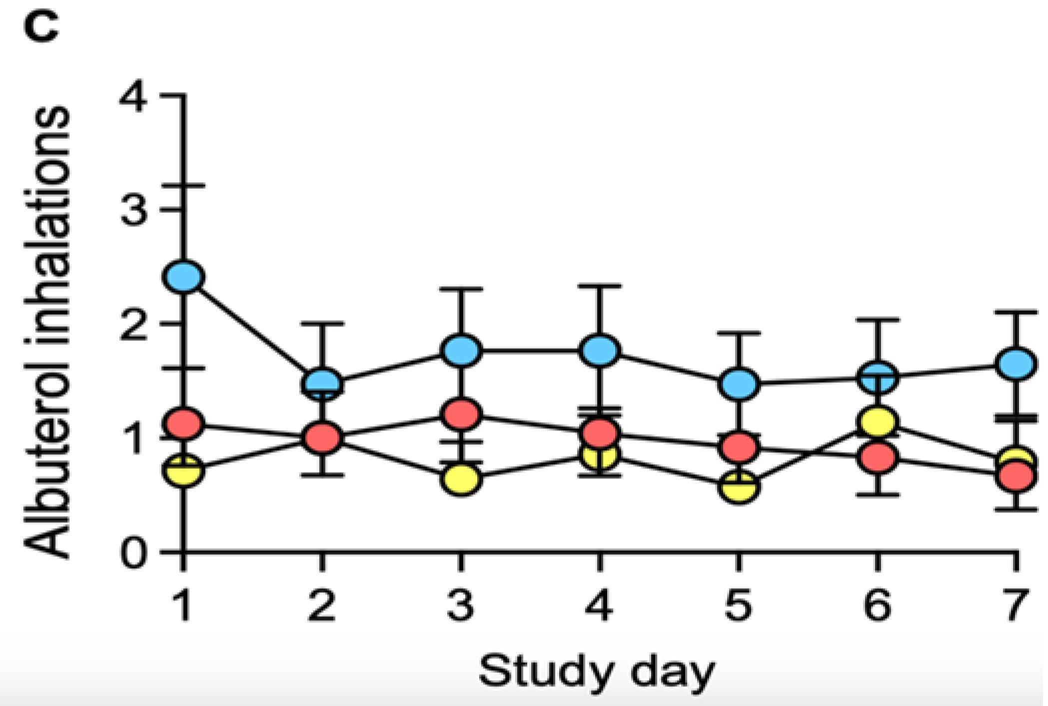
Obese
Non-Obese

Forno E, et al. J Allergy Clin Immunol 2011;127:741-9.

Decreased Systemic Steroid Response

7 days after triamcinolone





Fitzpatrick AM, et al. J Allergy Clin Immunol Pract 2022;10:815-26.

Reasons for Potential Poor Response

- Inflammatory phenotype (low TH2)
- Location of inflammation (systemic vs airway)
- Mechanical changes in lungs

POLL QUESTION

What percentage of hospitalized overweight/obese children with asthma had a documented weight management plan?

A) 5%
B) 8.3%
C) 12%
D) 15%

Starting Small

- 5-10% weight loss could improve asthma control and QoL (adult studies)
- Only 8.3% of overweight/obese children hospitalized for asthma had a treatment plan for weight documented

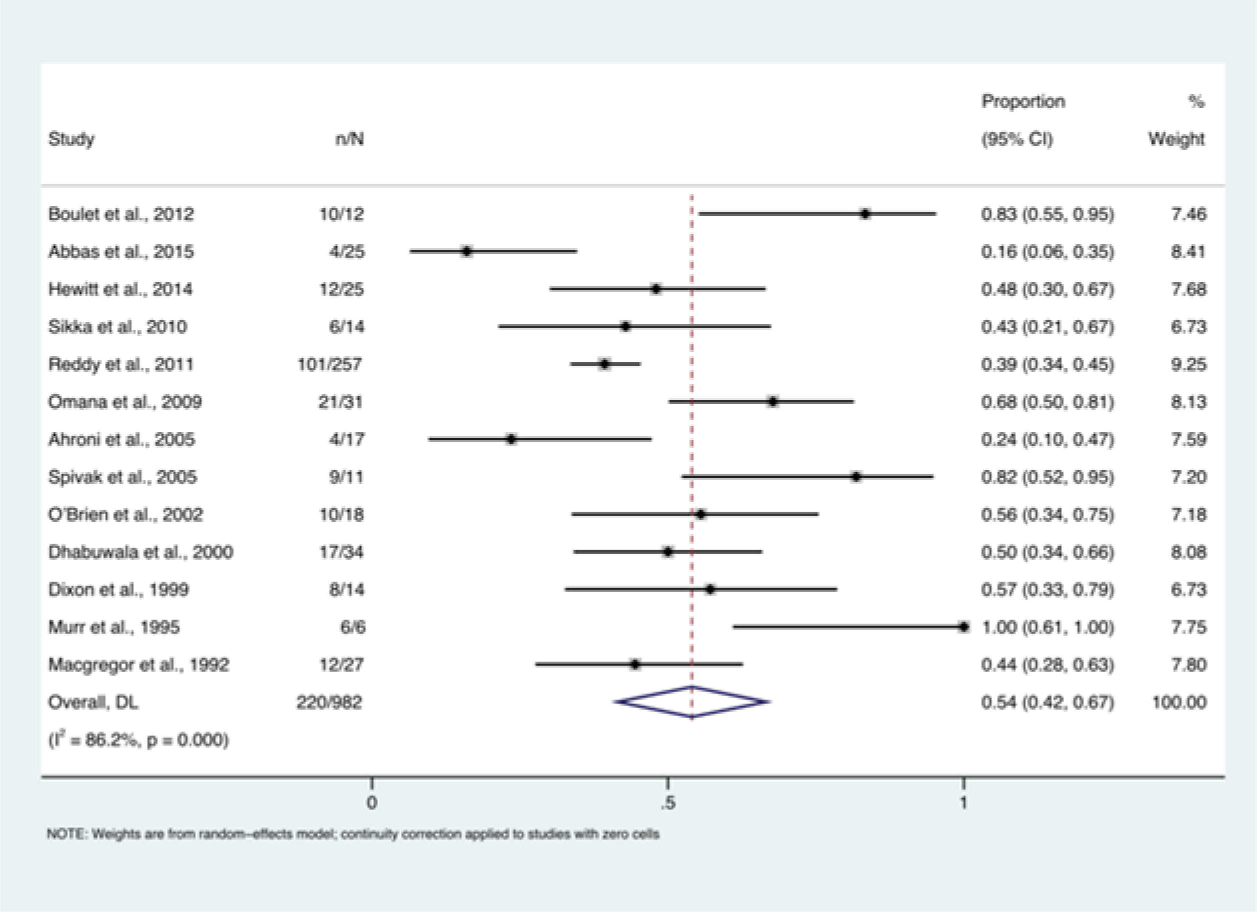
Borgmeyer A, et al. Hosp Pediatr 2016;6(11):667-76.
Scott HA, et al. Clin Exp Allergy 2013;43(1):36-49.
Willeboordse M, et al. PLoS ONE 11(6):e0157158.

Weight Loss Interventions in Asthma

Study	Intervention	Control	Results
Willebordse et al 2016	Lifestyle sessions, parental and individual sessions, regular sports sessions, CBT	Usual care	• No between group difference in weight loss • Improved FVC • Improved within group ACT and PAQLQ
Luna-Pech et al 2014	Normo-caloric diet	Free diet	• Significant between group weight loss • No difference in FEV1 • Improved PAQLQ • Decreased SABA use with intervention
Abd El-Kader et al 2013	Diet regimen and exercise training	Usual care	• Significant between group weight loss • Decreased TNF-alpha, leptin, IL-6, IL-8
Jensen et al 2013	Dietitian counseling and targeted calorie reduction	Usual care	• Significant between group weight loss • No difference in PFTs between groups • Reduced CRP • Improved ACQ

Okoniewski W, et al. Ann Am Thorac Soc 2019;16:613-25.

Bariatric Surgery in Adults



Proportion of asthma medications discontinuation after bariatric surgery

- 54% completely discontinued asthma therapies
- 22-46% reduction in asthma therapies
- Possible over- or mis-diagnosis of asthma

Xie L, et al. Obesity Reviews 2023;24:e13527.

Metabolic Syndrome + Bariatric Surgery

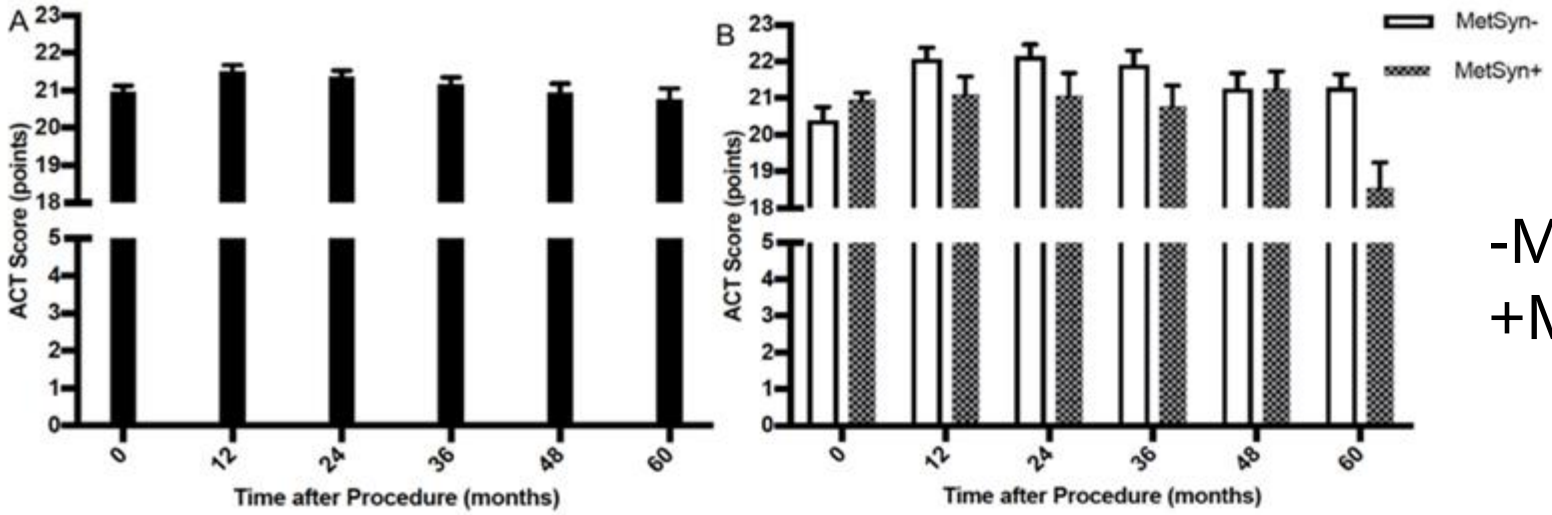


Fig 2. Mean ACT score at baseline and following bariatric surgery.

ACT Score

-MetSyn: 20.4 □ 21.3
+MetSyn: No improvement

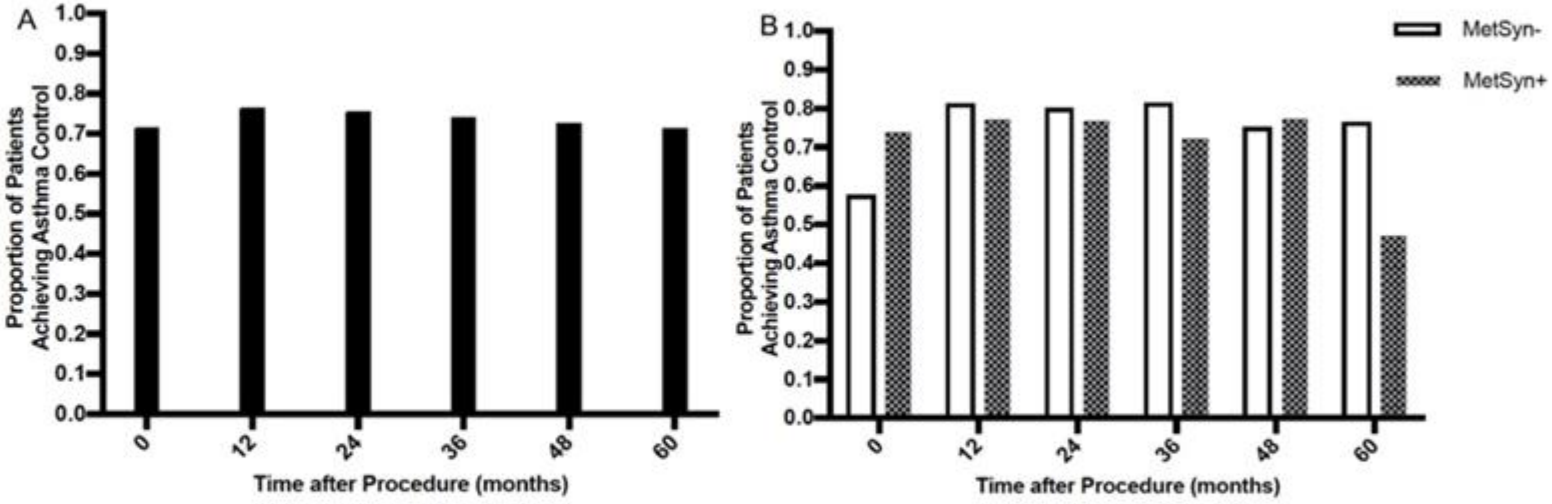


Fig 3. Proportion of patients achieving asthma control at baseline and following bariatric surgery.

ACT ≥19

-MetSyn: 58% □ 82%
+MetSyn: 74% □ 47%

Forno E, et al. PLoS ONE 2019;14:e0214730.

GLP-1R Agonists

Diabetes Management

- Lowers blood glucose
  - Stimulate endogenous insulin secretion
  - Suppress glucagon secretion
- Slows gastric emptying, reduces food intake
- Moderates postprandial hyperglycemia, normalizes fasting hyperglycemia

Potential Role in Asthma

- Inhibit allergy inflammation
  - Decrease lung IL-33, eosinophilia, and ILC2 proliferation after allergen challenge
  - Decreased ILC2 IL-5 and IL-13 secretion
- Relieve airway obstruction
  - Mitigate bronchial hyperresponsiveness after allergen challenge

Wu AY, et al. Curr Opin Allergy Clin Immunol 2022;22:36-41

Asthma & DM Treated by GLP-1R

Table 2. Primary and Secondary Asthma Outcomes by Type 2 Diabetes Treatment Groups

	Asthma Exacerbations			Asthma Symptoms		
Treatment Groups*	**Incidence Rate Ratio**	**95% CI**	***P* Value**	**Incidence Rate Ratio**	**95% CI**	***P* Value**
GLP-1R (*n* = 448)	ref	—	—	ref	—	—
SGLT-2 inhibitor (*n* = 112)	2.98	1.30–6.80	0.01	1.44	0.72–2.88	0.30
DPP-4 inhibitor (*n* = 435)	2.45	1.54–3.89	<0.001	1.71	1.14–2.57	0.009
Sulfonylurea (*n* = 2,253)	1.83	1.20–2.77	0.005	1.73	1.21–2.47	0.003
Basal insulin (*n* = 2,692)	2.58	1.72–3.88	<0.001	1.89	1.35–2.65	<0.001

Table 3. Sensitivity Analysis for Asthma Exacerbations Outcome, Inclusive of Baseline and Change in HbA_{1c} and BMI

	Asthma Exacerbations		
Treatment Groups*	**Incidence Rate Ratio**	**95% CI**	***P* Value**
GLP-1R (*n* = 271)	ref	—	—
SGLT-2 inhibitor (*n* = 74)	2.95	1.19–7.31	0.02
DPP-4 inhibitor (*n* = 224)	2.11	1.14–3.91	0.02
Sulfonylurea (*n* = 1,007)	1.97	1.14–3.41	0.02
Basal insulin (*n* = 1,015)	2.44	1.42–4.19	0.001

Foer D, et al. Am J Respir Crit Care Med 2021;203:831-40.

Take Home Points

- Obesity-related asthma is a unique phenotype where metabolic dysfunction and underlying inflammation are more important to pathology than mass/weight.
- Guidelines-based therapy should be used for the initial treatment of obese pediatric patients with asthma, but they may be less responsive to ICS.
- Weight loss strategies have been associated with improved quality of life, SABA use, asthma control, and inflammation.
- Studies are needed to explore the efficacy of bariatric surgery and GLP-1R agonists in pediatric patients, but limited adult studies show benefit.

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Children's Hospital Colorado
Here, it's different.

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