

Childhood Obesity and Risk of Allergy or Asthma



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KEYWORDS

• Obesity • Asthma • Allergy • Airway inflammation • Adipokines

KEY POINTS

- There has been a simultaneous increase in the prevalence of obesity and allergic disorders in children, suggesting a possible link between the two.
- Obesity is associated more often with nonatopic asthma than atopic asthma, suggesting noneosinophilic inflammation and Th1 polarization.
- The evidence for the role of obesity in the augmentation of other allergic disorders is conflicting.
- The mechanisms of obesity-associated asthma possibly include deranged lung function, systemic/airway inflammation influenced by adipokines, comorbidities, and shared factors (diet, sedentary lifestyle, and genetics).

INTRODUCTION

Allergic diseases are the most common chronic diseases in children around the world. The prevalence of allergic diseases especially asthma has been found to be increasing over last 2 decades.^{1,2} The prevalence of obesity has also increased tremendously over last 3 decades.³ A simultaneous increment in the prevalence of both obesity and asthma/allergic diseases suggests a possible link between the two. Despite data suggesting the epidemiologic link between asthma and obesity, the relationship remains unclear and many confounders (gender, ethnicity, genetic factors, and comorbidities) are likely to influence the obesity–asthma link.

The aim of the current review was to focus on the consequences of obesity on allergic diseases, especially asthma in children and adolescents, and to evaluate the available evidence on the possible mechanisms.

EPIDEMIOLOGY OF OBESITY AND ALLERGIC DISEASES IN CHILDREN

In the National Health and Nutrition Examination Survey (NHANES) for 2009 through 2010, the prevalence of obesity was 16.9% in US children and adolescents (18.6%

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in boys and 15.0% in girls).³ Since 1980, the prevalence of obesity in children and adolescents has tripled. Asthma prevalence in children and adolescents (0–17 years) has increased from 3.6% in 1980 to 9.5% in 2008 through 2010.¹ The prevalence of allergic diseases (food and skin allergies) has similarly increased from 1997 to 2011 in children younger than 18 years in the United States.² Both asthma and obesity are more prevalent in children from low socioeconomic strata and minority populations.^{1,3}

Prospective, population-based studies have shown an increased risk of incident asthma in children and adults with a greater body mass index (BMI).^{4–8} Gender-based differences have been observed in some studies, with a stronger association between BMI and asthma among girls compared with boys.^{4,9–11} Reports from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three study involving 6- and 7-year-olds from 17 countries, and 13- and 14-year-olds from 35 countries, have shown significant association between overweight/obesity and asthma/eczema symptoms, but not with rhinoconjunctivitis.¹² Data from developing countries are still lacking on the association between obesity and asthma in children. We have been following a pediatric asthmatic cohort over last 5 years; the mean BMI of 240 children in this cohort was $15.3 \pm 2.6 \text{ kg/m}^2$, with only 2% overweight and obese individuals.

A recent population based longitudinal study assessing health records of 623,358 patients aged 6 to 19 years suggested that obese individuals are not only at risk of asthma, but also more likely to have severe asthma, resulting in greater health care utilization, asthma exacerbations, and aggressive asthma treatment.¹³

OBESITY AND RISK OF ATOPY/ALLERGY

Evidence is conflicting on the potential role of obesity on the development of allergy or atopy in childhood. The data from the NHANES III (1988–1994) showed significant association between BMI and asthma, but no association between BMI and atopy (as defined by positive skin prick testing) after adjusting for confounders.¹⁴ Subsequent reports from the NHANES for 1998 through 2006 survey found a stronger association between obesity and current asthma in nonatopic children (odds ratio [OR], 2.46; 95% CI, 1.21–5.02) than atopic children (OR, 1.34; 95% CI, 0.70–2.57).¹⁵ A large, multicenter, cross-sectional study of adults (aged 20–44 years) did not find any association between raised BMI and atopy (sensitization to dust mite, cat, grass, specific immunoglobulin [Ig]E against these allergens, and total IgE).¹⁶

Similarly, a large, multicenter, cross-sectional study from 8 Spanish cities concluded that obese schoolchildren (6- and 7-year-olds) were at a greater risk of nonallergic asthma than nonobese subjects, whereas the risk of allergic asthma was similar.¹⁷ This was a questionnaire-based study and the authors used rhinoconjunctivitis as a marker of atopy. A study of Portuguese schoolchildren found increased prevalence of overweight/obesity in atopic children compared with nonatopic children.¹⁸

Gender has also been found to affect the relationship between obesity and atopy. Collective data from Caucasian Australian children suggested that higher BMI was associated with an higher prevalence of atopy in girls only.¹⁹ A somewhat similar observation has been made in a birth cohort study from New Zealand.²⁰ The cohort was evaluated at various occasions between age 9 and 26 years. A higher BMI was associated with asthma and atopy in women only. BMI has also been associated with increased prevalence of atopy and allergic symptoms in Taiwanese adolescent girls.²¹

As evident from these studies, there is no consistent evidence of association between obesity and atopy. The obesity–asthma relationship is also stronger in nonatopic asthma compared with atopic asthma, with possible effect modification by gender. The association of obesity with markers of allergic inflammation, like peripheral eosinophil counts and exhaled nitric oxide, is also not consistent. The studies are also heterogeneous in terms of definition of allergy or atopy, using self-reported allergic symptoms, parental questionnaires, skin prick testing, specific IgE levels, or total IgE levels.

The association between allergic diseases other than asthma and obesity is conflicting and not as consistent as the obesity–asthma link. A study in Japanese school children based on ISAAC questionnaires reported a positive relationship between obesity and asthma prevalence, and allergic dermatitis severity, but negative associations between obesity and allergic rhinitis and allergic conjunctivitis.²² A large, retrospective, case control study in US children and adolescents with atopic dermatitis found a positive relation between obesity and atopic dermatitis (OR, 2.0; 95% CI, 1.22–3.26; $P = .006$).²³ The association was present when obesity started before 2 years of age but absent beyond 5 years of age. Differently, a study of Belgian school-children found no relation between BMI and allergic symptoms (respiratory, eczema, and rhinoconjunctivitis).²⁴

To summarize, the association between BMI and allergic disorders other than asthma is conflicting and is possibly modified by age, gender, ethnicity, and type of disease. The association between BMI and eczema is fairly consistent. However, there is no/inverse relationship between BMI and allergic rhinitis/rhinoconjunctivitis.

Table 1 summarizes the results of various studies evaluating the relation between obesity and allergic disorders.

IS OBESITY A CAUSE OR EFFECT OF ASTHMA: CAUSALITY AND REVERSE CAUSALITY?

The hypothesis of asthma preceding obesity is supported by the evidence that asthmatics receive frequent steroid bursts, are likely to exercise less fearing asthma symptoms, stay more indoors leading to increased exposure to indoor air pollution, and pursue a sedentary lifestyle. A prospective community based cross-sectional study of young adults followed up between 20 and 40 years found an association between asthma and obesity.³³ However, longitudinal follow-up of the cohort revealed that asthma preceded weight gain and subsequent obesity. Obesity was not associated with subsequent asthma. Childhood depressive symptoms possibly contributed to a major part of the asthma–obesity relation in this study. The authors stressed the role played by psychological factors during childhood, which may influence the obesity–asthma relationship in adolescence and adults. Further, there are data using Granger causality tests relating past asthma diagnosis with subsequent obesity.³⁴

The evidence evaluating the obesity–asthma link in children has to be viewed carefully, because there are plaguing issues pertaining to definitions of asthma and obesity. Most of the studies have defined asthma using self- or parent-reported symptoms or physician-diagnosed asthma. Few studies have used stringent asthma diagnosis, including bronchodilation or bronchoprovocation tests. Similarly, obesity has been variously defined. Although most studies use BMI as a marker for adiposity using the World Health Organization definition of BMI as greater than 30 kg/m² or greater than the 95th percentile, other studies have used weight, weight for height z-score, waist circumference, conicity index, percent body fat, and skin fold thickness. The lack of uniformity in the definition of asthma and obesity is likely to affect the interpretation of the results and adds to the heterogeneity of evidence.

Table 1
Summary of studies evaluating the relation between obesity and allergy

Author, ^{Ref} Year Country	Studied	Sample Size/Study Population	Definition of Atopy	Summary of Findings
Fenger et al, ²⁵ 2012 Denmark	Association between different adiposity measures and asthma/atopy/lung function	Population based study 3471 persons, 19–72 y	Specific IgE	All measures of adiposity associated with asthma (stronger in nonatopics than atopics)
Cibella et al, ²⁶ 2011 Italy	Association between BMI and FENO/allergic sensitization	Cross-sectional epidemiologic study 708 children (10–16 y)	Skin prick tests, FENO	BMI not associated with high FENO, but independently related to asthma/allergic sensitization
Silverberg et al, ²³ 2011 US	Association between obesity and atopic dermatitis	Retrospective, case-control study: 414 persons (1–21 y) with atopic dermatitis 828 healthy controls	Atopic dermatitis based on diagnostic criteria	Obesity was associated with increased risk and severity of atopic dermatitis
Visness et al, ¹⁵ 2010 US	Association between obesity and asthma in atopic and non atopic individuals	NHANES (2005–2006) 3387 individuals (1–19 y)	Specific IgE	Association stronger in nonatopics than atopics
Musaad et al, ²⁷ 2009 US	Association of measures of obesity with allergic asthma	Cross-sectional case control study 1123 children (5–18 y)	Skin prick tests	Negative association between obesity and allergic sensitization among asthmatics
Spathopoulos et al, ²⁸ 2009 Greece	Association of obesity with asthma/atopy	Cross-sectional study 2715 children (6–11 y)	Questionnaire based	High BMI independent risk factor for asthma/atopy
Chen et al, ²⁹ 2009 Canada	Association between obesity and asthma in atopic and nonatopic individuals	Cross-sectional study 1997 adults (18–79 y)	Skin prick tests	Association between obesity and asthma stronger in nonatopics
Gysel et al, ²⁴ 2009 Belgium	Association between BMI categories and atopy	Cross-sectional study 1576 children (3.4–14.8 y)	Skin prick tests	No difference in sensitization between normal weight and obese/overweight

Leung et al, ³⁰ 2009 China	Association between adiposity markers and asthma/atopy	Cross-sectional study 486 school children	Specific IgE	No association between obesity and asthma/atopy
Ross et al, ³¹ 2009 US	Evaluation of the risk factors and comorbidities in children with asthma and obesity	Cross-sectional study 116 children (4–18 y)	Skin prick tests or specific IgE	No difference in proportion of atopy in obese and nonobese individuals
Garcia-Marcos et al, ¹⁷ 2008 Spain	Effect modification of allergy on asthma obesity relationship	Cross-sectional study 17,145 school children (6–7 y)	Presence of rhinoconjunctivitis based on questionnaires	Obese children at increased risk of nonallergic asthma than nonobese children
Silva et al, ¹⁸ 2007 Portugal	Association between BMI and atopic disease	Cross-sectional study 112 with atopy, 116 without atopy (5–16 y)	ISAAC questionnaire based diagnosis of asthma, AR, allergic eczema	Overweight/obesity more prevalent in atopic children
Hancox et al, ²⁰ 2005 New Zealand	Relationship between BMI, asthma, and atopy	Prospective birth cohort of 1037 children followed for ≤ 26 y	Skin prick tests	Increased BMI associated with asthma and atopy in females only
Tantisira et al, ³² 2003 US	Relationship of BMI with measures of asthma severity	Baseline data of CAMP study (an RCT) 1041 children (5–12 y)	IgE and eosinophil counts	No association of atopy with BMI
Jarvis et al, ¹⁶ 2002 16 countries	Association between BMI and respiratory symptoms/atopy	ECRHS 13,909 adults (20–44 y)	Specific and total IgE	No association between BMI and atopy
von Mutius et al, ¹⁴ 2001 US	Association of BMI with asthma/atopy	NHANES III (1988–1994), 7505 children (4–17 y)	Skin prick tests	After adjustment for confounders only asthma, not atopy, related to BMI

Abbreviations: AR, Allergic rhinitis; BMI, body mass index; CAMP, Childhood Asthma Management Program; ECRHS, European Community Respiratory Health Survey; FENO, fractional exhaled nitric oxide; Ig, immunoglobulin; ISAAC, International Study on Asthma and Allergy in Childhood; NHANES, National Health and Nutrition Examination Survey; RCT, randomized, controlled trial.

With many prospective studies from different countries, it has been observed that obesity is likely to precede asthma in most scenarios. However, there remains a likelihood of a subgroup of children (especially the early onset phenotype) in which asthma might precede obesity.

POSSIBLE MECHANISMS OF ASTHMA IN THE OBESE CHILDREN

The obesity–asthma link is complex and likely to be affected by many confounders. Obesity affects the lungs in multiple ways. These include changes in lung mechanics, augmentation of airway inflammation, common genetic basis, inflammatory effects of adipokines and cytokines, increased airway hyperresponsiveness, decreased physical activity, and effects of obesity related comorbidities (gastroesophageal reflux disease [GERD], sleep-disordered breathing [SDB]; **Box 1**).^{35–37}

ADIPOKINES AND SYSTEMIC INFLAMMATION IN OBESITY: DO THESE AGGRAVATE OR CAUSE ASTHMA?

The adipose tissue in the obese is involved in the release of certain hormones (leptin, adiponectin, and resistin)³⁸ and cytokines (tumor necrosis factor- α , interleukin [IL]-6). These hormones and cytokines might be responsible for insulin resistance, hypertension, cardiovascular morbidities, metabolic disorders, and asthma related to obesity. Whether these adipokines and cytokines are involved in modifying the risk of asthma in obese children remains unclear.

Box 1
Proposed mechanisms responsible for obesity–asthma link

1. Inflammation

- Adipokines (leptin, adiponectin, resistin, C-reactive protein, tumor necrosis factor- α , interleukin-6)
- Airway inflammation
- Oxidative stress

2. Lung mechanics

- Reduced lung volumes
- Poor lung function
- Airway closure

3. Comorbidities

- Gastroesophageal reflux disease
- Sleep-disordered breathing
- Dyslipidemia

4. Physical deconditioning/increased perception of dyspnea

5. Shared genetic factors

6. Shared life style factors

- Diet
- Decreased exercise
- Sedentary lifestyle

7. Hormonal influences/puberty

Leptin, a product of the *ob* gene expressed predominantly in adipose tissue, is among the most studied proinflammatory adipokines. Serum levels of leptin are markedly increased in obesity. Leptin has effects on the innate and adaptive immune responses. Evidence suggests that high leptin levels are associated with higher asthma prevalence in prepubertal boys³⁹ and peri- and postpubertal girls.⁴⁰ High serum leptin concentrations are associated with increased severity of exercise-induced bronchoconstriction⁴¹ and low peak expiratory flow rate⁴² in children.

Adiponectin predominantly has antiinflammatory properties. It inhibits the production and effects of proinflammatory cytokines like tumor necrosis factor- α and IL-6. It induces the expression of antiinflammatory cytokines like IL-1 receptor antagonist and IL-10. However, it also exerts proinflammatory properties under certain conditions. Adiponectin levels are inversely related to BMI and obesity, and increase with weight loss.³⁸ Presence of adiponectin and receptors in lung suggest their possible role in the asthma–obesity link.

Animal studies have shown that adiponectin treatment markedly reduces allergen-induced airway inflammation and hyperresponsiveness.⁴³ Low serum adiponectin levels are associated with increased asthma prevalence and future risk of asthma in women.^{44,45} High serum adiponectin levels have been associated with adverse clinical outcomes of asthma (more frequent active disease, frequent asthma medication use) in men but in not women.⁴⁶ A prospective study involving 368 urban adolescents with moderate to severe asthma showed that adiponectin levels were inversely related to severity of asthma status (asthma symptoms and exacerbations) and positively related to forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC).⁴⁷ Serum adiponectin levels are also significantly negatively correlated with exercise-induced bronchoconstriction in children.⁴¹

Resistin is a proinflammatory adipokine, and derives its name from its ability to resist insulin (“resistance to insulin”). Few data are available on the role of resistin in asthma. One Korean study revealed that atopic childhood asthmatics had lower resistin levels compared with nonatopic asthmatics and control group.⁴⁸ It also demonstrated that resistin correlated positively with methacholine PC(20) and negatively with eosinophil count and total IgE. These findings suggest that resistin might have a protective role in asthma.

DOES CHILDHOOD OBESITY PROMOTE MIXED T HELPER CELL TYPE 1/2 INFLAMMATION?

Because adiposity is characterized by low-grade systemic inflammation, it is possible that adiposity influences allergic disorders through effects on the immune response. Individuals with allergic disorders usually have a T helper cell type 2 (Th2) polarization. A number of studies have tried to assess the Th polarization in obese subjects.

In a study involving obese asthmatic children, nonobese asthmatic children, obese nonasthmatic children, and nonobese nonasthmatic children, it was found that obese asthmatic children had significantly higher Th1 responses to a mitogen–phorbol 12-myristate 13-acetate and tetanus toxoid and lower Th2 responses to phorbol 12-myristate 13-acetate and *Dermaphagoides farinae* compared with nonobese asthmatic children.⁴⁹ Th cell patterns did not differ between obese asthmatic children and obese nonasthmatic children.⁴⁹ It is possible that adipokines skew the Th1/Th2 balance in favor of the Th1 response seen in asthma associated with obesity.^{50,51} Further, this could also explain the reason for the poor association of obesity with other allergic disorders, which have a predominant Th2 response.

ARE OBESE CHILDREN AT HIGHER RISK OF HAVING AIRWAY HYPER-RESPONSIVENESS?

Airway hyperresponsiveness (AHR) is a characteristic feature of asthma. Many studies have been conducted in children and adults with conflicting evidence on the role of obesity in enhancing or modifying airway responsiveness. AHR has been assessed using methacholine, histamine, or exercise. Cross-sectional data analysis of the Childhood Asthma Management Program on 1039 US children aged 5 to 12 years suggested no effect of BMI on AHR after adjusting for baseline FEV₁.³² A prospective birth cohort study from New Zealand on 1037 children followed for 26 years found no effect of BMI on AHR.²⁰ A Korean cross-sectional study found increased AHR in obese versus nonobese boys but not girls.⁵² Likewise, a Taiwanese cross-sectional study on adolescents suggested that AHR increased with BMI, but only in girls.²¹ All of these studies used methacholine as the bronchoconstricting agent. Even as AHR assessed using methacholine or histamine shows conflicting evidence, reports on exercise-induced bronchospasm are more consistent. These few small studies assessing exercise-induced bronchospasm have found greater severity of exercise-induced bronchospasm in obese versus nonobese children.^{41,53}

LUNG FUNCTION IN OBESE ASTHMATICS

Increased body fat exerts direct mechanical effects on the respiratory system and reduces lung volumes. The most prominent and consistent effect of obesity is a reduction in expiratory reserve volume (ERV) and functional residual capacity (FRC). Evidence from a large adult study of 373 patients with normal FEV₁/FVC ratio, showed a consistent decline in all lung volumes (especially FRC and ERV) with an increase in BMI from 20 to 30 kg/m².⁵⁴

Obese individuals breathe at low tidal volumes and high respiratory rate. Breathing at low FRC with low tidal volumes, decreases airway caliber, and thereby increases airway resistance. Lower FRC unloads the airway smooth muscle, which makes it liable to shorten more when stimulated by bronchoconstricting agents or parasympathetic tone.⁴³ It has also been observed that obese individuals breathe close to their closing volumes, making it prone to more frequent opening and closing, causing lung damage.

In contrast with the consistent observation for lung volumes in obese children, the effect of obesity on lung function is not consistent in studies. However, most studies show a decrease^{32,47,55} or no change^{26,56} in FEV₁/FVC ratio with increasing BMI. The conflicting studies in children could also be explained by the distribution of BMI among the participants. With a more normal distribution of BMI, lung function is likely to have a positive relationship with BMI. On the other hand, predominantly obese subjects with markedly high BMI are likely to have poorer lung function.

Spirometry parameters are affected by many factors, the most important of which are age, height, weight, gender, and race.⁵⁷ However, because it is lean muscle mass that is actually responsible for the increments in lung function rather than fat mass, BMI, which takes into account both lean and fat mass, may not be an appropriate surrogate of adiposity to assess a relationship between increasing fat mass and lung function. The effect of gender on the pattern of lung growth and fat deposition may be responsible for the differing patterns of lung function abnormalities seen in males and females.

OBESITY AND ASTHMA-RELATED OUTCOMES

Although many studies in adults have evaluated asthma-related outcomes (asthma control, severity, and exacerbations), pediatric data are limited. A large retrospective

study of more than 32,000 US children and adolescents found increased usage of β -agonists and corticosteroids in obese/overweight asthmatics even after adjustment for confounders and comorbidities.⁵⁸ Similarly, data from the GALA II and SAGE II studies showed that poor asthma control was associated with increased BMI, but only in boys, who had a 33% greater chance of worse asthma control as compared with normal-weight boys.⁵⁹ Another prospective study of 368 adolescents with moderate-to-severe asthma demonstrated that high BMI was associated with poorer asthma control (increased symptom days and risk of exacerbation) in females only.⁴⁷ Obese asthmatics with acute, severe asthma admitted to pediatric intensive care units have been found to recover more slowly than the nonobese counterparts.⁶⁰

On the other hand, a retrospective study found no difference in the usage of controller medications, steroid bursts, and FEV₁/FVC among different weight group asthmatic children (normal weight, overweight, and obese).³¹ A prospective study evaluating 108 children and adolescents in a specialty asthma clinic found no association between obesity and asthma severity.⁶¹

To summarize, there is evidence to suggest that obese asthmatics have more symptoms, use quick relief medications more often, have poorly controlled asthma, and recover more slowly from acute exacerbations.

ROLE OF COMORBIDITIES

Obesity and asthma are both associated with certain comorbidities like SDB and GERD, which may be responsible, partly, for the said association between the two. There are few studies in children that have assessed the role and temporal relationship of these comorbidities in the obesity–asthma link.

A large, community-based study evaluated the relationship between obesity, SDB, and wheezing.⁶² The authors demonstrated that both obesity and SDB were associated with wheeze/asthma. Another study demonstrated that SDB was associated with higher exhaled nitric oxide values in obese children compared with normal weight or overweight controls.⁶³

GERD is associated with both asthma and obesity. Treatment of GERD is known to improve asthma control. Theoretically, GERD could partly explain the challenges of asthma control observed in obese individuals. A New Zealand birth cohort of 1037 individuals followed to 26 years of age found association of GERD with respiratory symptoms, independent of BMI.²⁰ Results from the European Community Respiratory Health Survey, which enrolled 2661 adults aged 20 to 48 years from 3 countries, found a strong association between nocturnal reflux symptoms and not only asthma and respiratory symptoms, but also obstructive sleep apnea⁶⁴; the association was independent of BMI. A follow-up questionnaire survey of the European Community Respiratory Health Survey participants evaluated obesity, nocturnal reflux, and habitual snoring as risk factors for asthma onset.⁶⁵ The study demonstrated that onset of asthma, wheeze, and night-time symptoms were associated with obesity, nocturnal reflux, and habitual snoring.

To summarize, GERD and SDB are related to both obesity and asthma. However, the causality and temporal relationship of these comorbidities in the obesity–asthma link is not yet established.

WEIGHT LOSS AND ASTHMA CONTROL

The causal relation of obesity and incident asthma can be confirmed by the improvement in asthma outcomes with weight loss. A recent, small, prospective randomized controlled trial reported that weight reduction in obese individuals with severe

uncontrolled asthma was associated with improved asthma control but no reduction in airway inflammation or bronchial hyperresponsiveness.⁶⁶ A study on weight loss using multidisciplinary intervention involving 76 obese adolescents (50 with and 26 without asthma) reported significant improvement in lung function.⁶⁷ The asthmatics demonstrated improvement in adiponectin levels, and reduction in C-reactive protein and leptin levels. Change in adiponectin emerged as an independent factor for improved lung function.

A systematic review evaluating weight loss and asthma demonstrated a consistent improvement in at least one asthma-related outcome in all 15 eligible studies.⁶⁸ Standard asthma management protocols now mention weight loss as a part of therapy in obese/overweight individuals.⁶⁹

SUMMARY

Obesity affects different allergic diseases in different ways. The strongest association of obesity has been with nonallergic asthma compared with allergic asthma. Because eosinophilic inflammation has not been shown to increase in obese asthmatics, the mechanisms are likely to be other than augmentation of Th2 responses. The evidence of association with allergic diseases other than asthma is conflicting. The association is more consistent with eczema, but poor or inverse with allergic rhinitis/rhinoconjunctivitis, the conditions in which Th2 pathways play a major role. The association between asthma and obesity is also modified with comorbidities like SDB and GERD. The strength of association between asthma and obesity makes the need of weight loss as a part of standard asthma care and management.

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