Obesity and asthma

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Obesity is a vast public health problem and both a major risk factor and disease modifier for asthma in children and adults. Obese subjects have increased asthma risk, and obese asthmatic patients have more symptoms, more frequent and severe exacerbations, reduced response to several asthma medications, and decreased quality of life. Obese asthma is a complex syndrome, including different phenotypes of disease that are just beginning to be understood. We examine the epidemiology and characteristics of this syndrome in children and adults, as well as the changes in lung function seen in each age group. We then discuss the better recognized factors and mechanisms involved in disease pathogenesis, focusing particularly on diet and nutrients, the microbiome, inflammatory and metabolic dysregulation, and the genetics/genomics of obese asthma. Finally, we describe current evidence on the effect of weight loss and mention some important future directions for research in the field. (J Allergy Clin Immunol 2018;141:1169-79.)

Key words: Asthma, obesity, obese asthma, metabolic syndrome, microbiome

Obesity is both a major risk factor and a disease modifier of asthma in children and adults. Although obesity is defined according to a threshold body mass index (BMI), recent studies suggest that BMI *z* scores might be unreliable, particularly among children and adolescents with severe obesity.[1-3] In adults obesity is defined as a BMI of 30 kg/m^2 or greater, yet a given BMI might reflect vastly differing physiology and metabolic health. This distinction is likely important for asthma. Although serum IL-6 (produced by macrophages in adipose tissue and a marker of metabolic health) is a marker of asthma severity, some subjects with BMIs in the nonobese range have increased IL-6 levels[4]; Sideleva et al[5] found that adipose tissue inflammation is increased in obese patients with asthma compared with obese control

Abbreviations used

AHR:	Airway hyperresponsiveness
BMI:	Body mass index
CAMP:	Childhood Asthma Management Program
ERV:	Expiratory reserve volume
FVC:	Forced vital capacity
ICS:	Inhaled corticosteroid
ILC:	Innate lymphoid cell
NO:	Nitric oxide
RCT:	Randomized controlled trial
SCFA:	Short-chain fatty acid
SNP:	Single nucleotide polymorphism
TLC:	Total lung capacity

subjects. Metabolic dysfunction is more important than fat mass for asthma in obesity; however, most asthma studies have used BMI and metabolic dysfunction related to obesity synonymously. In this article we will report data on metabolic dysfunction, where available, but will otherwise use obesity as a marker of both fat mass and metabolic dysfunction.

EPIDEMIOLOGY OF OBESITY AND CHILDHOOD ASTHMA

Asthma affects approximately 6.5 million children (approximately 9% prevalence) in the United States.[6] Likewise, 17% of children in this country are obese, and another 15% are overweight.[7] Obesity is now recognized as a major risk factor for asthma: several longitudinal epidemiologic studies show that obesity or increased adiposity often precedes incident asthma.[8-16] Many studies have reported differing obesity-asthma associations by sex,[10,17-20] although results on which sex is more affected have been conflicting. Obesity is also associated with increased asthma severity.

Obesity-induced increases in asthma risk can start *in utero*. In a meta-analysis of more than 108,000 participants, we found that maternal obesity and weight gain during pregnancy are independently associated with approximately 15% to 30% increased risk of asthma in the offspring, and others have reported very similar findings.[21,22] This risk is not merely mediated by the child's own obesity.[23] Mechanisms involved can include inflammatory or other changes during pregnancy or early postnatal life,[24-26] and these mechanisms might explain why excessive weight gain in infancy has also been linked to recurrent wheezing and asthma.[27,28]

EPIDEMIOLOGY OF OBESITY AND ASTHMA IN ADULTS

A meta-analysis of several prospective studies involving more than 300,000 adults found a dose-response relationship between obesity and asthma: the odds ratio of incident asthma was 1.5 in the overweight and 1.9 in the obese groups compared with the lean group; in effect, 250,000 new asthma cases per year in the United States are related to obesity.[29] This relationship has radically changed the demographics of asthma in the United States: the prevalence of asthma in lean adults is 7.1%, and that in obese adults is 11.1%. The relationship is more striking in women; the prevalence of asthma in lean versus obese women is 7.9% and 14.6%, respectively.[30]
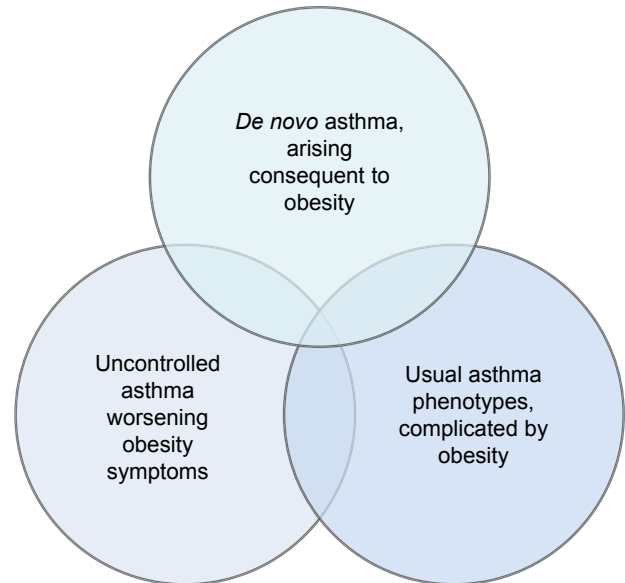
FIG 1. Obese asthma syndrome. The syndrome of obese asthma likely includes many phenotypes: those typically seen in lean subjects, now complicated by obesity; disease newly arising in obese subjects; and perhaps a separate phenotype characterized by increased response to environmental pollutants. Much work remains to be done to understand whether these are unique phenotypes that require individualized therapeutic approaches.

CLINICAL CHARACTERISTICS OF OBESE ASTHMA IN CHILDREN

On occasion, asthma can predispose to obesity,[31] obesity can confound its diagnosis,[32,33] or both can simply co-occur. However, the majority of observational and experimental evidence points to an "obese asthma" phenotype in which obesity modifies asthma.[34,35]

Obese children tend to have increased asthma severity,[36-38] poorer disease control,[39] and lower quality of life.[40] Many obese children with asthma tend to have T_H1-skewed responses, particularly in response to inflammatory stimuli, with at least part of these responses mediated by systemic inflammation, insulin resistance, and/or alterations in lipid metabolism.[41-43] These children and adolescents also tend to have a decreased response to asthma medications. Using data from the Childhood Asthma Management Program (CAMP), we described that overweight and obese children with asthma had a reduced response to inhaled corticosteroids (ICSs), leading to increased prednisone courses and moderate-to-severe exacerbations.[44] More recently, McGarry et al[45] reported that obese black and Latino adolescents were 24% more likely to be bronchodilator unresponsive than their nonobese peers. Moreover, among children hospitalized for asthma, obesity is associated with longer length of stay and higher risk of mechanical ventilation.[37] Obese children with asthma might also be more susceptible to having increased symptoms with exposure to indoor pollutants.[46]

CLINICAL CHARACTERISTICS OF OBESE ASTHMA IN ADULTS

Much like children, obese adults tend to have more severe asthma than lean adults, with a 4- to 6-fold higher risk of being hospitalized compared with lean adults with asthma.[47] Nearly 60% of adults with severe asthma in the United States are obese.[48] Obese patients also have worse asthma control and lower quality of life.[49] Obese asthmatic patients do not respond as well to standard controller

Biomarkers
- Leptin ↑ [↓]
- Adiponectin ↓ [↑]
- Adipose tissue inflammation ↑ [↓]
- Serum IL-6 ↑ [↓]
- Oxidative stress ↑ [↓]
- Exhaled nitric oxide ↓ [*]

Clinical Findings
- Risk of incident asthma ↑ [↓]
- Risk of asthma exacerbation ↑ [↓]
- Asthma severity ↑ [↓]
- Asthma control ↓ [↑]
- Asthma quality of life ↓ [↑]
- Treatment response ↓ [↑]
- Susceptibility to air pollutants ↑ [↓]

Lung Function and airway reactivity
- FEV_1 ↓ [↑]
- Expiratory reserve volume ↓ [↑]
- Functional residual capacity ↓ [↑]
- Peak expired flow ↓ [↑]
- Airway hyperresponsiveness ↑ [↓]
- Bronchodilator responsiveness ↔ [*]

FIG 2. Effect of obesity on biomarkers and clinical outcomes of asthma in adults. Proposed pathways that have been found to be altered in obesity and asthma in adults are shown. *Solid arrows* indicate the effect of obesity. *Dashed arrows inside brackets* indicate changes that have been seen after weight loss. *Pathway has not been studied or no significant associations have been reported.

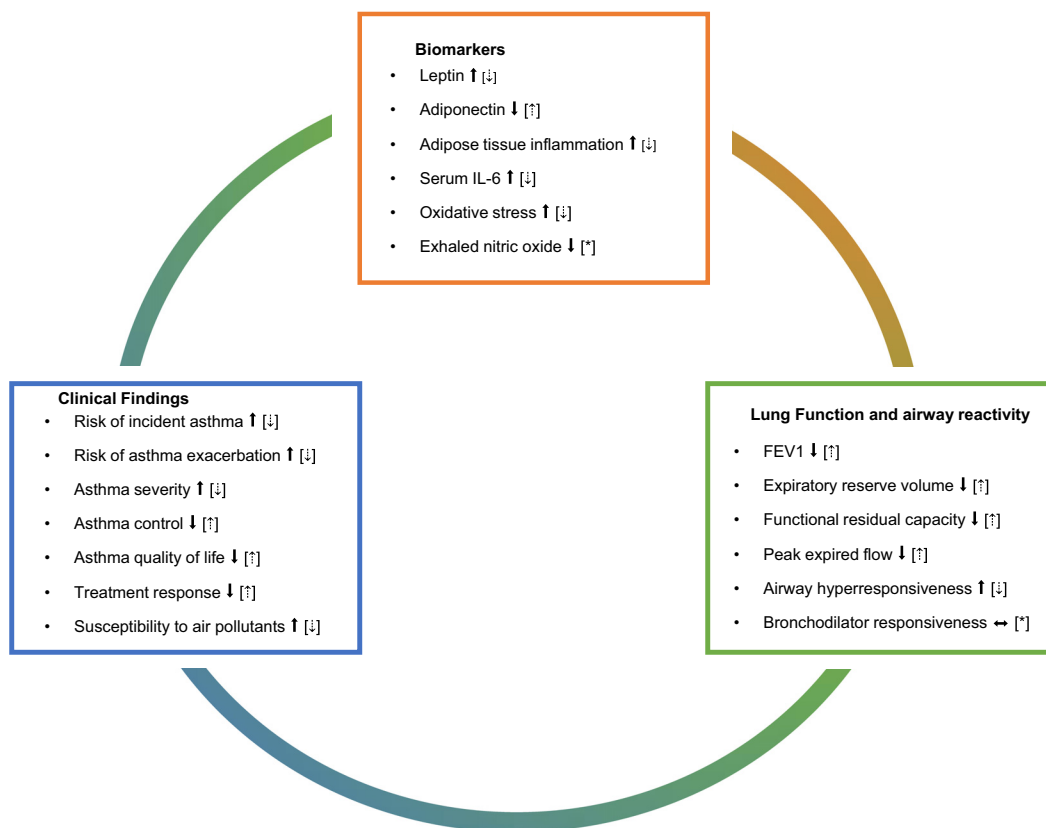medications, such as ICSs and ICS/long-acting β-agonist combination.[50] The mechanisms behind the impaired ICS response are likely related to increased production of inflammatory cytokines in obesity, which reduce induction of mitogen-activated kinase phosphatase 1 by glucocorticoid, a signaling protein that plays an important role in steroid responses.[51] Impaired response to asthma therapy in obesity is also due to the altered pathogenesis of disease, which does not respond well to medications developed to treat conventional allergic asthma.

There are likely several phenotypes within the obese asthma syndrome (Fig 1). Holguin et al[47] reported that obese asthmatic patients with earlier-onset disease (who tended to have higher markers of T_H2 inflammation) had the most severe disease among obese asthmatic patients. There is also a group with later-onset disease, most often female, with little in the way of airway inflammation but significant inflammation in adipose tissue and increased airway oxidative stress.[5] Some have described a phenotype with neutrophilic airway inflammation,[52] which improves with weight loss in women.[53] Obese subjects appear to have increased susceptibility to air pollutants,[54,55] which has been elegantly modeled in animals.[56] Whether this contributes to a distinct phenotype or complicates other phenotypes is not yet clear.

OBESITY AND LUNG FUNCTION IN PEDIATRIC PATIENTS

Childhood obesity has a significant effect on lung function. Although our initial understanding of this phenomenon derived

from studies in adults (described in the following section), as early as 1997, Lazarus et al[57] reported that height-adjusted FEV_1 and forced vital capacity (FVC) were greater in children with higher weight. Tantisira et al[58] described that BMI was associated with higher FEV_1 and FVC but a lower FEV_1/FVC ratio among participants in CAMP.[58] In a recent meta-analysis including dozens of studies, we reported that childhood obesity is associated with normal or higher FEV_1 and FVC but a lower FEV_1/FVC ratio.[59]

Recently, we described that childhood obesity is associated with airway dysanapsis, an incongruence between growth of the lung parenchyma and airway caliber that is reflected in normal or supranormal FEV_1 and FVC but with larger effects on FVC that lead to a low FEV_1/FVC ratio.[60] Obese children with asthma and dysanapsis had increased symptoms, medication use, and asthma exacerbations.

Many studies of spirometric lung function have found differential associations based on sex. In the study by Tantisira et al,[58] the decrease in FEV_1/FVC ratio with BMI was more pronounced in boys than in girls. Accordingly, we found that the risk of dysanapsis from obesity was greater in boys. However, others have found stronger obesity–lung function associations in girls.

Similarly, age is a critical factor. In a large meta-analysis of 24 birth cohorts, den Dekker et al[61] showed that greater birth weight and faster infant weight gain was associated with greater FEV_1 and FVC but a lower FEV_1/FVC ratio in school-aged children. Conversely, Strunk et al[62] reported that CAMP participants who were not obese during the trial but became obese later on had

significant decreases in FEV_1 and FEV_1/FVC ratio (compared with participants who were never obese) at approximately 26 to 30 years of age, with no significant associations with FVC. This is consistent with data in adults: obese patients with early-onset asthma have more severe airflow limitation than obese adults with late-onset asthma.[47]

The effect of childhood obesity on lung volume has been less studied, with only a handful of reports that have described conflicting findings. Davidson et al[63] reported that obese nonasthmatic children had lower functional residual capacity, residual volume, and expiratory reserve volume (ERV) than their nonobese counterparts. Rastogi et al[64] recently reported similar findings, further describing associations with insulin resistance and reduced high-density lipoprotein levels. However, others have reported higher total lung capacity (TLC) in obese adolescents, and yet others have reported no significant associations.[65,66] Similarly, it is not clear whether obesity leads to changes in airway hyperresponsiveness (AHR) in children, with some studies reporting higher[67] and others lower AHR.[68]

LUNG FUNCTION AND AHR IN OBESE ADULTS

Obesity causes significant changes to normal lung physiology in adults (Fig 2). Excessive accumulation of fat in the thoracic and abdominal cavities leads to lung compression and an attendant reduction in lung volume.[69] The most notable changes include a reduction in functional residual capacity and ERV.[70-72] Radial traction of lung parenchymal attachments around the airways is attenuated at low lung volumes,[73] which might contribute to airway collapse. Indeed, we have shown that obesity increases collapsibility of the peripheral airways and parenchyma, especially among asthmatic patients with late-onset disease.[74]

AHR is a distinguishing feature of asthma. The only prospective longitudinal cohort study that investigated the relationship between obesity and AHR in more than 7000 adults reported that the risk for AHR increases with BMI and that weight gain was a risk factor for AHR.[75] Some smaller studies did not find a consistent relationship between AHR and obesity[76,77]; this might be related to small sample sizes or differences between patient populations.

Misdiagnosis of asthma is common, but no more common in obese than nonobese patients. Aaron et al[78] conducted a prospective study of 540 patients with physician-diagnosed asthma, and after rigorous assessment with bronchial reversibility and methacholine challenge and withdrawal of asthma medication, they concluded that 31.8% of obese and 28.7% of nonobese patients given a diagnosis of asthma were actually misclassified as having asthma.[78] Diagnosis of asthma should be confirmed by using physiologic testing in both lean and obese patients with respiratory symptoms.

THE ROLE OF DIET

Specific micronutrients might be involved in the association between obesity and asthma. Obesity is associated with low circulating vitamin D levels.[79] Vitamin D deficiency might be a risk factor for the development of both obesity and asthma: prenatal vitamin D insufficiency has been associated with obesity in the offspring,[80] and prenatal vitamin D supplementation led to a small decrease in the risk of wheezing illness at age 3 years (although this did not reach formal statistical significance).[81,82] This could be highly significant for asthma in obesity; there is a growing literature on the association between vitamin D

deficiency and the risk of respiratory tract infections, asthma exacerbations,[83] and corticosteroid resistance,[84] and therefore vitamin D deficiency might predispose to the development of obesity and then to a phenotype of increased asthma severity and corticosteroid resistance. The efficacy of supplementation of vitamin D specifically on asthma in obesity is not known.

Diets that promote obesity, such as the Western diet pattern, tend to be high in saturated fatty acids, low in fiber and antioxidants, and high in sugars, such as fructose. There is a growing literature on the harmful effects of these specific dietary components on asthma. Ingestion of a single meal high in saturated fatty acids increases neutrophilic airway inflammation and decreases bronchodilator responsiveness.[85] Animal studies suggest that a high-fat diet increases the number of innate lymphoid cells (ILCs) in the lung and can induce both innate AHR and allergic airway inflammation through an IL-1β pathway.[86,87] Supplementation with a high-versus low-antioxidant diet for 14 days (but not an antioxidant supplement) improved spirometric lung function and increased subsequent time to asthma exacerbation, although this has not been studied specifically in obese asthma.[88] Studies in a mouse model of asthma suggest that a diet high in fructose promotes systemic metabolic dysfunction and increases AHR and airway oxidative stress.[89] There are few studies of dietary interventions promoting healthy dietary patterns in obese asthmatic patients, although a recent pilot study suggests that this approach might constitute an alternative to simply promoting weight loss.[90]

Specific dietary and nutritional risk factors can affect children. Breast-feeding has been associated with lower risks of both obesity and asthma.[91,92] Beverages containing high sugar levels are a risk factor for asthma,[93] as is a diet poor in vegetables and grains but rich in sweets and dairy products.[94] Omega-3 has been associated with lower incidence of asthma, whereas omega-6 fatty acids are associated with higher risk of asthma in pediatric subjects.[95,96]

The studies described above implicate dietary factors as potentially having direct effects on the airways, but it is also possible that diet could have indirect effects on the airway through effects on the gut microbiome.

THE MICROBIOME AND PATHOPHYSIOLOGY OF OBESE ASTHMA

Dietary changes lead to alterations in the gut microbiome, and changes characteristic of a Western dietary pattern, which promotes obesity, might also affect the development of allergic airway disease. Bacterial colonization of the gut plays a key role in fermentation of dietary fiber and generation of short-chain fatty acids (SCFAs). Obesogenic diets are typically high in fat and low in soluble fiber; low fiber is associated with changes in the gut microbiome and circulating SCFA levels.[97] Bacteroidetes bacteria, a major producer of SCFAs, are reduced in the gut in obesity[98] and in the lungs of asthmatic patients.[99] A low-fiber diet decreases levels of the SCFA propionate; Trompette et al[100] showed that a low-fiber diet with low circulating propionate levels was associated with exaggerated allergic airway inflammation in a mouse model and that increasing propionate levels decreased the ability of dendritic cells to promote T_H2 responses and therefore attenuated allergic airway inflammation. Conversely, Thorburn et al[101] showed that a high-fiber diet increases levels of acetate, which inhibits the development of allergic airway inflammation in a mouse model through effects on histone deacetylase 9 and

regulatory T-cell function; this effect could also be seen in offspring of mice fed a high-fiber diet, likely through epigenetic modification of the forkhead box P3 promoter. The authors also reported that high serum acetate levels in women were associated with lower risk of allergic airway disease in children. These studies suggest that diets low in fiber lead to changes in the gut microbiome, which can promote both obesity and allergic asthma.

Another factor that could alter the microbiome is antibiotic exposure. Antibiotic exposure early in life has been associated with asthma[102] and obesity.[103] The leading theory is that early changes in the microbiome can alter the maturation of the immune system because anomalous responses to these changes have been reported to precede asthma and atopy.[104] Probiotic supplementation in early life (*in utero* and/or infancy) for the mother, infant, or both has been shown to reduce the risk of atopy but not asthma.[105]

The airway microbiome can be altered in obese asthmatic patients. A recent study in bronchial brushings from patients with severe asthma showed that BMI was associated with changes in airway microbial composition and fewer lung tissue eosinophils.[106] It is unclear whether these microbiome changes cause reduced eosinophil counts or are simply an unrelated consequence of other changes seen in obesity (eg, other immune derangements or increased gastroesophageal reflux).

INFLAMMATORY AND METABOLIC CHANGES IN OBESE ASTHMATIC PATIENTS

Many studies have reported that obesity-related asthma is more often nonatopic, yet some studies have reported that obesity in itself is associated with atopy.[107,108] In adolescents participating in the National Health and Nutrition Examination Survey, we found that obesity was associated with asthma only among participants with normal or low exhaled nitric oxide (NO; fraction of exhaled NO) levels; however, among those who already had asthma and high fraction of exhaled NO levels, obesity was associated with increased asthma severity.[109]

Classic T_H2 inflammation is complicated by the obese state. For example, eosinophilic airway inflammation is altered in obesity, with altered trafficking of eosinophils into the airway lumen; sputum eosinophil counts and exhaled NO levels might underestimate the degree of type 2 inflammation in obesity.[110] Obesity skews CD4 cells toward T_H1 polarization, which is associated with worse asthma severity and control and abnormal lung function.[42] It is worth noting that eosinophils, alternatively activated macrophages, and type 2 cytokines are thought to play an important homeostatic role in healthy adipose tissue, with infiltration of proinflammatory M1 macrophages and decreased eosinophil counts associated with the development of obesity and insulin resistance; how this relates to airway disease is not clear.[111,112]

Innate immune responses involving T_H17 pathways and ILCs have also been implicated.[86,87] ILCs play an important role in adipose tissue homeostasis, and thus changes in ILC function in obese adipose tissue could contribute to both obesity and asthma.[111,113] Macrophage activation by ILCs and other pathways might constitute an important link between adiposity and worse asthma outcomes.[114] In patients Zheng et al[115] reported increased sputum neutrophil counts in "nonatopic obese asthmatics," while subjects with "atopy-obesity overlap" exhibited higher sputum macrophage counts, suggesting the importance of these innate pathways in patients with obesity-related asthma.[115]
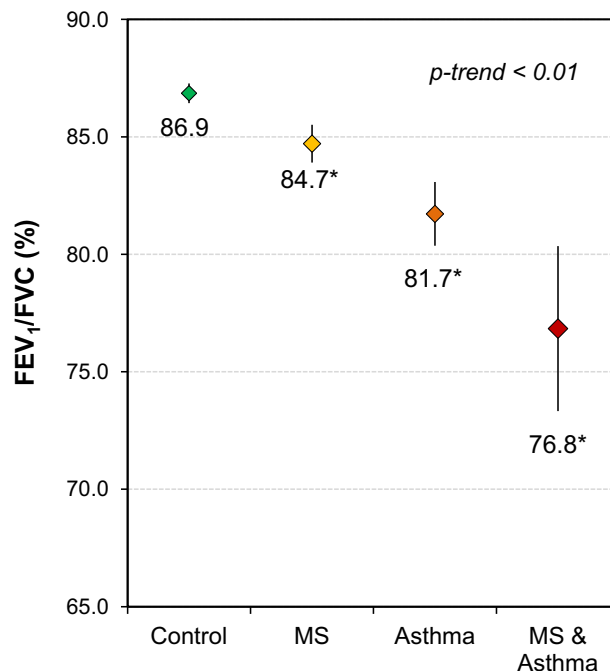
FIG 3. FEV_1/FVC ratio in adolescents with metabolic syndrome. Metabolic syndrome *(MS)* and asthma synergistically reduce FEV_1/FVC ratios in adolescents. Data are from the National Health and Nutrition Examination Survey. Models were adjusted for age, sex, race/ethnicity, health insurance, family history of asthma, tobacco smoke exposure, C-reactive protein level, and BMI *z* score. **P* < .05. Reproduced with permission from Forno et al.[129]

Changes in pulmonary innate immune function likely contribute to asthma in obese subjects. For example, bronchoalveolar fluid levels of surfactant protein A, which helps modulate the response to infectious and other insults, are lower in obese asthmatic patients compared with their lean counterparts, and mouse models have shown that administration of surfactant protein A reduces lung tissue eosinophilia after allergen challenge,[116] suggesting that changes in surfactant protein function could alter airway eosinophilia in obese asthmatic patients.

Adipokines and other cytokines produced or induced by adipose tissue can also affect the lungs and airways (Fig 2).[117,118] Higher leptin levels in obese adolescents correlate inversely with FEV_1, FVC, and FEV_1/FVC ratio,[41,119] and visceral fat leptin expression correlates with airway reactivity in adults.[5] Leptin and adiponectin have also been associated with exercise-induced changes in lung function.[120] Most existing literature is based on cross-sectional studies, and it is not clear whether adipokine levels can serve as biomarkers to identify at-risk patients and follow response to management or are pathogenic mediators of disease.

Metabolic dysregulation plays an important role in many complications of obesity, including asthma.[121,122] Hyperglycemia and hyperinsulinemia can contribute to AHR and remodeling through epithelial damage and airway smooth muscle proliferation.[123-125] The metabolic syndrome has been associated with asthma and lower lung function in adults.[126-128] Similarly, we reported previously that insulin resistance and metabolic syndrome are associated with lower lung function in adolescents with and without asthma (Fig 3).[129] Obesity-related proinflammatory cytokines, such as IL-6, can play a crucial role in the relationship between the metabolic syndrome, lung function, and asthma

TABLE I. Studies of lifestyle weight-loss interventions and asthma

Author	Year	No. of subjects	Groups/intervention	Main findings
Hakala et al[144]	2000	Fourteen adults (all with asthma)	Single-arm, very low-calorie diet, 8-wk intervention	Significant improvements in peak flow, spirometric results, and lung volumes; mean weight loss, 13.7 kg
Aaron et al[145]	2004	Fifty-eight women (24 with asthma)	Single-arm, meal replacement, 6-mo intervention	Significant improvement in spirometric results but not in AHR; mean weight loss, 20 kg
Johnson et al[146]	2007	Ten adults (all with asthma)	Single-arm, alternate-day caloric restriction, 2-mo intervention	Significant improvements in peak flow and asthma control but not in spirometric results; mean weight loss, 8% of baseline
van de Griendt et al[147]	2012	One hundred twelve children (8-18 y, all without asthma)	Single-arm, multidisciplinary weight-loss intervention for severely obese children; duration, 26 wk	FEV_1, TLC, and ERV improved; only ERV correlated with the reduction in BMI and waist circumference; mean weight loss, 13.9 kg
da Silva et al[148]	2012	Seventy-six adolescents (26 with asthma)	Single-arm, multidisciplinary weight-loss intervention, 1-y duration	Improvements in adipokine levels and lung function; improved asthma severity in the group with asthma
Scott et al[53]	2013	Forty-six adults (all with asthma)	Randomized to diet, exercise, or diet plus exercise groups; 10-wk intervention	Asthma control improved in diet and diet plus exercise groups; 5% to 10% weight loss was associated with improved asthma control
Jensen et al[149]	2013	Twenty-eight children (8-17 y, all with asthma)	Randomized to intensive dietary intervention vs wait-list control, 10-wk intervention	Improvements in ERV and asthma control in intervention group; mean weight loss, 3.4 kg
Luna-Pech et al[150]	2014	Fifty-one children (12-18 y, all with asthma)	Randomized to supervised normocaloric vs no intervention for 28 wk	Weight loss correlated with improved asthma control and quality of life; mean weight loss, 2.5 kg
van Leeuwen et al[151]	2014	Twenty children (8-18 y, all with asthma)	Single-arm, dietary intervention; duration, 6 wk	Improvement in quality of life and exercise-induced bronchoconstriction but not in asthma control; mean weight loss, 2.6% of baseline
Ma et al[152]	2015	Three hundred thirty adults (all with asthma)	Randomized to intensive dietary intervention vs educational intervention, 1-y study	Increased odds of improvement in asthma control in those who lost ≥10% weight
Pakhale et al[153]	2015	Twenty-two adults (all with asthma)	Single-arm, liquid meal replacement vs observation control; duration, 3 mo	Improvement in FEV_1, FVC, asthma control, and AHR; mean weight loss, 16.5 kg (14.2% of baseline)
Willeboordse et al[154]	2016	Eighty-seven children (6-16 y, all with asthma)	Randomized to multifactorial intervention vs usual care, 18-mo duration	Weight, lung function, and asthma outcomes improved in both groups; intervention had greater improvement in FVC and asthma control
Freitas et al[155]	2017	Fifty-five adults (all with asthma)	Randomized to dietary and exercise intervention vs diet only; duration, 3 mo	Diet and exercise caused more weight less than diet alone (6.8% vs 3.1%), greater improvements in asthma control and FENO

FENO, Fraction of exhaled nitric oxide.

severity.[4] Innovative approaches, such as breath condensate analytics using nuclear magnetic resonance, have recently identified distinct metabolic signatures in patients with obese asthma, suggesting unique pathogenic pathways compared with obesity or asthma alone.[130] Research is needed to determine whether pharmacologic management of the metabolic syndrome can lead to improvements in asthma outcomes. A recent retrospective study reported that metformin use was associated with improved asthma outcomes among patients with both diabetes and asthma,[131] although a prospective study of pioglitazone did not show efficacy in obese asthmatic patients.[132]

Increased oxidative stress occurs in obesity, and increased airway oxidative stress has been found particularly in obese adults with late-onset asthma.[133] This is thought to be related to reduction in the bioavailability of arginine, a substrate for the production of NO: NO is an endogenous bronchodilator, and therefore reduced NO bioavailability can contribute to airway disease in obese patients.[53] Altered adaptive and innate immune responses, adipose-related inflammation, and increased oxidative stress all likely contribute to asthma in obese patients.

GENETICS, EPIGENETICS, AND GENOMICS

Both asthma and obesity have a considerable hereditary component, and thus investigators have studied whether there are genetic variants that might represent a link; to date, these
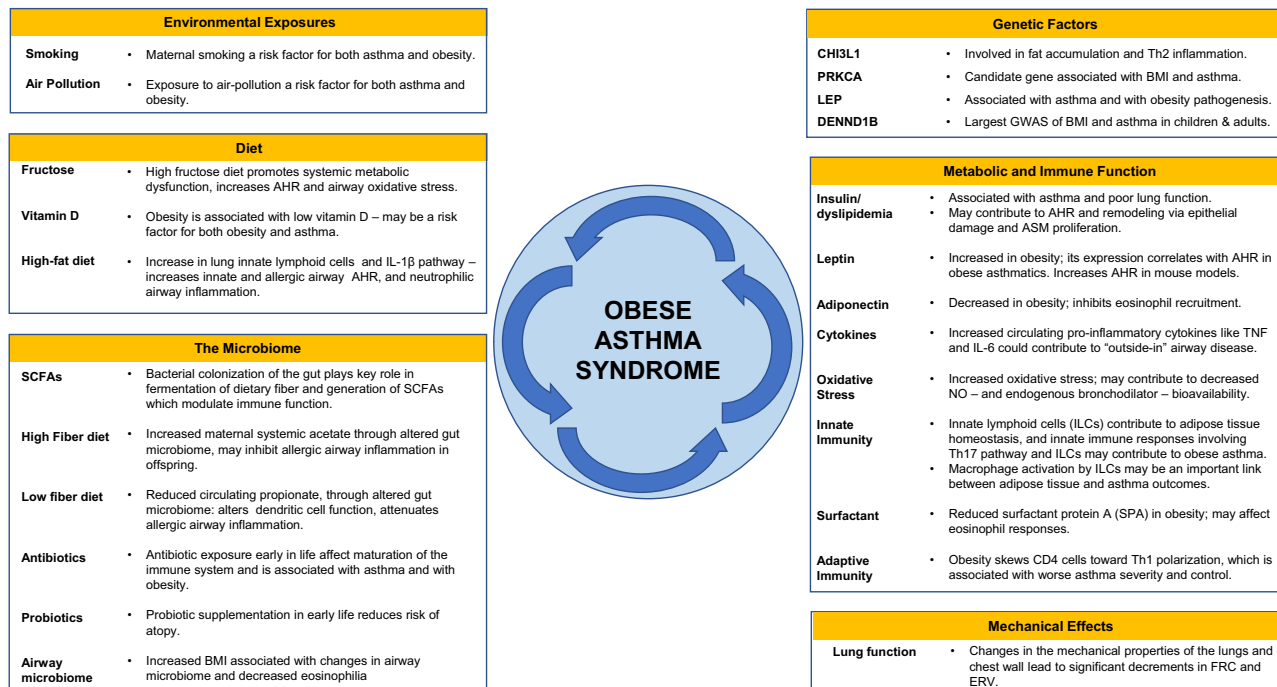
Environmental Exposures

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.

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.

The Microbiome

SCFAs	• Bacterial colonization of the gut plays key role in fermentation of dietary fiber and generation of SCFAs which modulate immune function.
High Fiber diet	• Increased maternal systemic acetate through altered gut microbiome, may inhibit allergic airway inflammation in offspring.
Low fiber diet	• Reduced circulating propionate, through altered gut microbiome: alters dendritic cell function, attenuates allergic airway inflammation.
Antibiotics	• Antibiotic exposure early in life affect maturation of the immune system and is associated with asthma and with obesity.
Probiotics	• Probiotic supplementation in early life reduces risk of atopy.
Airway microbiome	• Increased BMI associated with changes in airway microbiome and decreased eosinophilia

OBESE ASTHMA SYNDROME

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.

Metabolic and Immune Function

Insulin/ dyslipidemia	• Associated with asthma and poor lung function. • May contribute to AHR and remodeling via epithelial damage and ASM proliferation.
Leptin	• Increased in obesity; its expression correlates with AHR in obese asthmatics. Increases AHR in mouse models.
Adiponectin	• Decreased in obesity; inhibits eosinophil recruitment.
Cytokines	• Increased circulating pro-inflammatory cytokines like TNF and IL-6 could contribute to "outside-in" airway disease.
Oxidative Stress	• Increased oxidative stress; may contribute to decreased NO – and endogenous bronchodilator – bioavailability.
Innate Immunity	• Innate lymphoid cells (ILCs) contribute to adipose tissue homeostasis, and innate immune responses involving Th17 pathway and ILCs may contribute to obese asthma. • Macrophage activation by ILCs may be an important link between adipose tissue and asthma outcomes.
Surfactant	• Reduced surfactant protein A (SPA) in obesity; may affect eosinophil responses.
Adaptive Immunity	• Obesity skews CD4 cells toward Th1 polarization, which is associated with worse asthma severity and control.

Mechanical Effects

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

FIG 4. Factors contributing to the syndrome of obesity-related asthma. *ASM,* Airway smooth muscle; *FRC,* functional residual capacity; *GWAS,* genome-wide association study.

studies have been somewhat inauspicious. Candidate gene studies have reported a few genes associated with asthma and BMI, such as *PRKCA*, *LEP*, and *ADRB3*.[134-136] The largest pediatric genome-wide association study to date, which included more than 23,000 children and adults, reported on the gene *DENND1B*, although the main single nucleotide polymorphism (SNP) did not replicate in the independent cohorts.[137]

Other approaches have yielded more encouraging results. In a gene-environment analysis, Wang et al[138] found 7 SNPs in 17q21 (a well-known asthma-associated locus) were associated with BMI only among asthmatic patients in 2 independent cohorts. In a small pilot study in 32 children, Rastogi et al[139] described differential epigenome-wide DNA methylation patterns in children according to their obesity and asthma status. In a CD4$^+$ T-cell transcriptomic analysis, they also reported T_H1-related pathways that are differentially expressed in obese versus nonobese asthmatic children.[140] In addition, a study in mice and human subjects by Ahangari et al[141] found that expression of the *CHI3L1* gene can be induced by a high-fat diet and that its product (chitinase 3-like 1) might contribute to both truncal obesity and asthma symptoms. Thus although obese asthma might not be directly determined by genetic polymorphisms, it can be influenced by epigenetic or transcriptomic regulation.

Genetics have also allowed investigators to dissect the many potential factors that can confound the association between obesity and asthma, including socioeconomic status, lifestyle factors, and environmental exposures. Using a Mendelian randomization approach, Granell et al[142] constructed a weighted allele score using 32 SNPs known to be associated with BMI and demonstrated that the score was also associated strongly with asthma in school-aged children. Similarly, in adults Skaaby et al[143] used a score of 26 BMI-associated SNPs and found that BMI is related to higher risk of asthma and lower lung function.

LIFESTYLE WEIGHT-LOSS INTERVENTIONS

Studies published on the effects of various weight-loss interventions on asthma control find significant improvements in both asthma control and spirometric lung function with sufficient weight loss (Table I).[53,144-146,150-153,155,156] Interventions vary from liquid diet replacement to a more graduated dietary education approach. In adults it appears that weight loss of at least 5% is required to produce a significant improvement in asthma control.[152] Typically, this is associated with improvements in peak flow, spirometric lung function, and ERV. Studies that have produced the most weight loss appear to be associated with the most significant improvements in asthma control. Effects on AHR have been variable, with some studies,[153] but not all,[145] reporting significant improvements in airway reactivity; we speculate the reasons for these contrasting findings might be related to the different phenotypes of obese asthmatic patients.

Few studies have reported the effects on markers of airway inflammation. One recent study compared dietary intervention versus exercise plus dietary intervention and found improvements in exhaled NO with exercise plus dietary intervention[155]; however, it is not clear whether this was related to exercise (exercise can reduce allergic airway inflammation through effects on regulatory T-cell function[157]) or weight loss. Scott et al[53] reported a decrease in airway neutrophilic inflammation in proportion to gynoid fat loss in women (and reduction in saturated fatty acid intake in men).

Pediatric studies of weight-loss interventions for obesity and asthma are scarce. Noncontrolled studies have reported improvements in FEV$_1$, ERV, and TLC that correlate with BMI[147,151] and changes in adipokine levels that correlate with improvements in FEV$_1$ and FVC, as well as exercise-induced bronchoconstriction.[148] However, without control groups, all of these studies are limited to small-group before/after comparisons. In a recent

randomized controlled trial (RCT), a dietary intervention resulted in significant improvements in ERV, although the difference with the control group was not significant.[149] Conversely, another RCT in children with asthma reported a greater improvement in FVC in the intervention group compared with the control group, but BMI changes were similar in both groups; there were no differences in FEV_1/FVC ratio, ERV, or TLC.[154] Finally, in another RCT Luna-Pech et al[150] showed reduced exacerbations and improved quality of life.

BARIATRIC SURGERY

The effects of bariatric (weight-loss) surgery have been reported by a number of investigators.[158-160] It is the most effective intervention for producing sustained and significant weight loss, and all studies have reported highly significant improvements in asthma control, airway reactivity, and lung function (Fig 2). Bariatric surgery also has significant effects on asthma exacerbations. Hasegawa et al[161] studied 2261 patients with asthma using a population emergency department and in-patient sample database; bariatric surgery led to a nearly 60% reduction in risk of having an asthma exacerbation, with a baseline risk of asthma exacerbation in the population of approximately 22%. Reduced exacerbations might in part be related to effects on lung mechanics and airway reactivity, but because obesity is associated with worse outcomes related to viral and bacterial infections, such as influenza and bacterial pneumonia,[162,163] and impaired response to influenza vaccination,[164] it is also possible that significant weight loss might reduce the risk of certain infections that precipitate asthma exacerbations.

CONCLUSIONS

Obesity is an important risk factor for asthma and asthma morbidity, both in children and adults. Although there are many common pathophysiologic and clinical commonalities, certain characteristics differ between both age groups. This is a reflection of an obese asthma syndrome that is complex and multifactorial. Potential underlying mechanisms include a shared genetic component, dietary and nutritional factors, alterations in the gut microbiome, systemic inflammation, metabolic abnormalities, and changes in lung anatomy and function (Fig 4). There is growing evidence that weight-loss interventions also help improve asthma outcomes. Future studies should characterize obesity beyond BMI, considering other anthropometric indices and biomarkers, much like asthma is not phenotyped merely by the presence or absence of wheezing.

Future research should aim to (1) improve our understanding of the different mechanisms and pathways that underlie obese asthma; (2) identify subphenotypes that might have different pathophysiology and thus respond to different management strategies, as well as find biomarkers that might help identify these subgroups; (3) develop new therapies and treatment approaches for these patients; (4) phenotype metabolic dysfunction rather than just BMI in asthmatic patients; (5) investigate how to effectively implement lifestyle interventions targeting obese asthmatic patients; and (6) investigate how changes in the diet and microbiome can affect outcomes in asthmatic patients.

What do we know?

- Obesity is associated with increased asthma risk and morbidity.
- Obese asthma is a complex syndrome with many phenotypes, which can differ between children and adults.
- Factors and pathways implicated in patients with obese asthma include changes in lung function, alterations in diet and nutrients, metabolic dysregulation, microbiome changes, and differences in epigenetic/genomic regulation.

What is still unknown?

- How to accurately classify obese asthma phenotypes, both in children and adults
- Whether new therapies or approaches might be more successful for patients with obesity and asthma
- Whether early-life microbiome or immune alterations predispose subjects to both obesity and asthma

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