Obesity and Asthma

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Abstract

Obesity is a major risk factor for the development of asthma, and the prevalence of obesity is higher in people with asthma than in the general population. Obese people often have severe asthma—recent studies in the United States suggest that 60% of adults with severe asthma are obese. Multiple mechanisms link obesity and asthma, which are discussed in this article, and these pathways contribute to different phenotypes of asthma among people with obesity. From a practical aspect, changes in physiology and immune markers affect diagnosis and monitoring of disease activity in people with asthma and obesity. Obesity also affects response to asthma medications and is associated with an increased risk of co-morbidities such as gastroesophageal reflux disease, depression, and obstructive sleep apnea, all of which may affect asthma control. Obese people may be at elevated risk of exacerbations related to increased risk of severe disease in response to viral infections. Interventions that target improved dietary quality, exercise, and weight loss are likely to be particularly helpful for this patient population.

Keywords

- airway reactivity
- oscillometry
- exacerbation
- weight loss
- diet
- co-morbidities
- viral infection
- gastroesophageal reflux disease
- obstructive sleep apnea
- depression
- type 2 inflammation

The United States along with much of the world, is facing an unprecedented obesity epidemic. Obesity is a major risk factor for asthma and is particularly associated with severe asthma. Obesity likely alters the pathogenesis of asthma and leads to novel disease phenotypes which require careful evaluation to guide treatment. The purpose of this article is to review the epidemiology and pathogenesis of obesity-associated asthma and provide data to inform a practical approach for the treatment of asthma in people with obesity.

Epidemiology

Asthma is classically described as a chronic inflammatory lung disease characterized by reversible airway inflammation and recurrent episodes of wheezing, cough, shortness of breath, and chest tightness. Asthma affects people of all ages. An estimated 25 million people in the United States are living with asthma, including 6 million children.[1] Asthma imparts a tremendous economic burden on patients, their families, and on society. In 2017, 1.8 million people visited an emergency department for asthma-related care and 189,000 people were hospitalized with asthma.[2]

The prevalence of asthma is rising and has increased from 7.3% in 2001 to 9.3% in 2017.[2] Although asthma affects all people, it disproportionately affects children and vulnerable populations such as low income, Hispanic and African American populations.[1] Indeed, in 2018 asthma prevalence was 40% higher for non-Hispanic blacks than non-Hispanic whites.[3]

According to the latest World Health Organization (WHO) Global Health Observatory data, the global prevalence of obesity is increasing worldwide at an alarming rate.[4,5] Body mass index (BMI), defined as the weight in kilograms divided by the square of the height in meters, is often used to define obesity in adults with BMI of 30 kg/m^2 or greater, and BMI between 25 and 30 kg/m^2 used to define overweight status.

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A growing body of evidence links asthma and obesity. Epidemiologic studies suggest that obesity increases both the prevalence and incidence of asthma.[6–10] In some individuals, obesity precedes asthma, and obesity is a risk factor for the later development of asthma.[6] In other individuals, asthma precedes obesity, suggesting that asthma may be a risk factor for the development of obesity. Indeed asthma at the age of three to four years is reported to increase the risk of obesity nearly twofold by age eight.[8] With obesity rates climbing, approximately 50% of Americans are predicted to be obese by 2030.[11] This is alarming as obesity rates are higher amongst adults with asthma.[9] Indeed the odds of being obese in people with asthma is estimated to be 1.75 compared with those without asthma.[7,9] Furthermore, there is a dose-dependent effect of obesity on the risk of asthma, such that the greater the BMI, the greater the risk of asthma. Compared with lean individuals, the risk of asthma is increased 1.4-fold for adults with a BMI of 30.0 to 34.9 kg/m^2 and 2.5-fold for adults with a BMI of 50 kg/m^2 and greater.[10]

The increased prevalence of obese asthma in adults is accompanied by a similar increase in obese asthma prevalence in children.[12] Studies suggest that the link between obesity and asthma begins *in utero*. Maternal obesity and weight gain during pregnancy are independently associated with as much as a 30% increased risk of asthma in offspring.[13,14] Data are accumulating to show that obese children have a higher chance of developing asthma: in a study of more than 500,000 children, obese youth had a 26 to 38% increased risk of asthma,[12] and an estimated 23 to 27% of new asthma cases in children with obesity were found to be directly attributable to obesity. In the absence of overweight and obesity, it is estimated that 10% of all cases of pediatric asthma could potentially be avoided. Treatment for asthma may exacerbate obesity: a study from Sweden reported that inhaled corticosteroid (ICS) use in the first 6 years of life was associated with increased risk of obesity.[15] This suggests that obesity is a risk factor for asthma in children, and that treatment for asthma may contribute to obesity, which might then worsen both conditions.

In the United States, asthma prevalence is higher in obese women (14.6%) than in lean (7.9%) or overweight (9.1%) women.[14] Similar findings were not present in men.[14] Among adults with severe asthma, nearly 60% are obese.[5]

Obese Asthma Phenotypes

Hierarchical supervised cluster analyses of large clinical datasets first identified obese asthma as a unique phenotype with cluster 2 in the Leicester asthma study and cluster 3 in the Severe Asthma Research Program (SARP).[16,17] In both studies, the obese asthma phenotype shared common characteristics including late onset disease, female sex, less atopy, and increased asthma burden. More recent studies suggest that there are at least two distinct phenotypes of asthma in the obese patient: early onset obese asthma (age of onset <12 years) which is characterized by atopy and type 2 inflammation with airway eosinophilia and mucus hypersecretion[18–20] and late onset obese asthma, which predominates in females, is non-eosinophilic with normal type 2 biomarkers and has less airway obstruction.[19,21] Our understanding of obese asthma phenotypes is evolving, and there are likely to be multiple different phenotypes of obese asthma, depending on both the endotype of airway disease, and the endotype of obesity.

Pathophysiology

To understand the pathophysiology of asthma in people with obesity, one first needs to appreciate the normal expected effects of obesity on pulmonary function to distinguish the pathophysiologic changes characteristic of obesity and asthma (►**Table 1**, ►**Fig. 1**).

Physiology

Obesity affects lung growth, increasing lung size as measured by spirometry: obese children have increased forced expiratory volume in one second (FEV_1) and FVC compared with lean children. However, there is not simply increased growth, there is *disproportionate* growth: the luminal area of the airway does not increase at the same rate as the rest of lung, leading to decreased airway diameter relative to length. This disproportionate growth produces physiologic airflow limitation, by decreasing the ratio of FEV_1 to FVC, a phenomenon known as airway dysanapsis.[22] Airway dysanapsis likely contributes to the development of airflow limitation in obese children, and so may contribute to asthma-type physiological changes.

In adults with obesity, FEV_1 and FVC decrease uniformly.[23] This uniform decrease in FEV_1 and FVC is related in part to

Table 1 Normal effects of obesity on lung function versus physiological characteristics of asthma in obesity

Normal effects of obesity on lung function	Characteristics of obese asthma
In children: increased FVC relative to FEV_1, airway dysanapsis	Airway dysanapsis may contribute to physiologic airflow limitation
Decreased FEV_1, FVC (related to insulin resistance)	Increased peripheral lung stiffness
Expiratory dynamic collapse of large airways	Small airway collapse and air trapping during exhalation
Small airway collapse and atelectasis during exhalation	Rapid shallow breathing induced by bronchoconstriction suggesting impaired ability to recruit close airways
Airway closure contributes to V/Q mismatch	Increased closing index during induced bronchoconstriction
	Dissociation between biomarkers and airway type 2 inflammation

Abbreviations: FEV, forced expiratory volume; FVC, forced vital capacity.

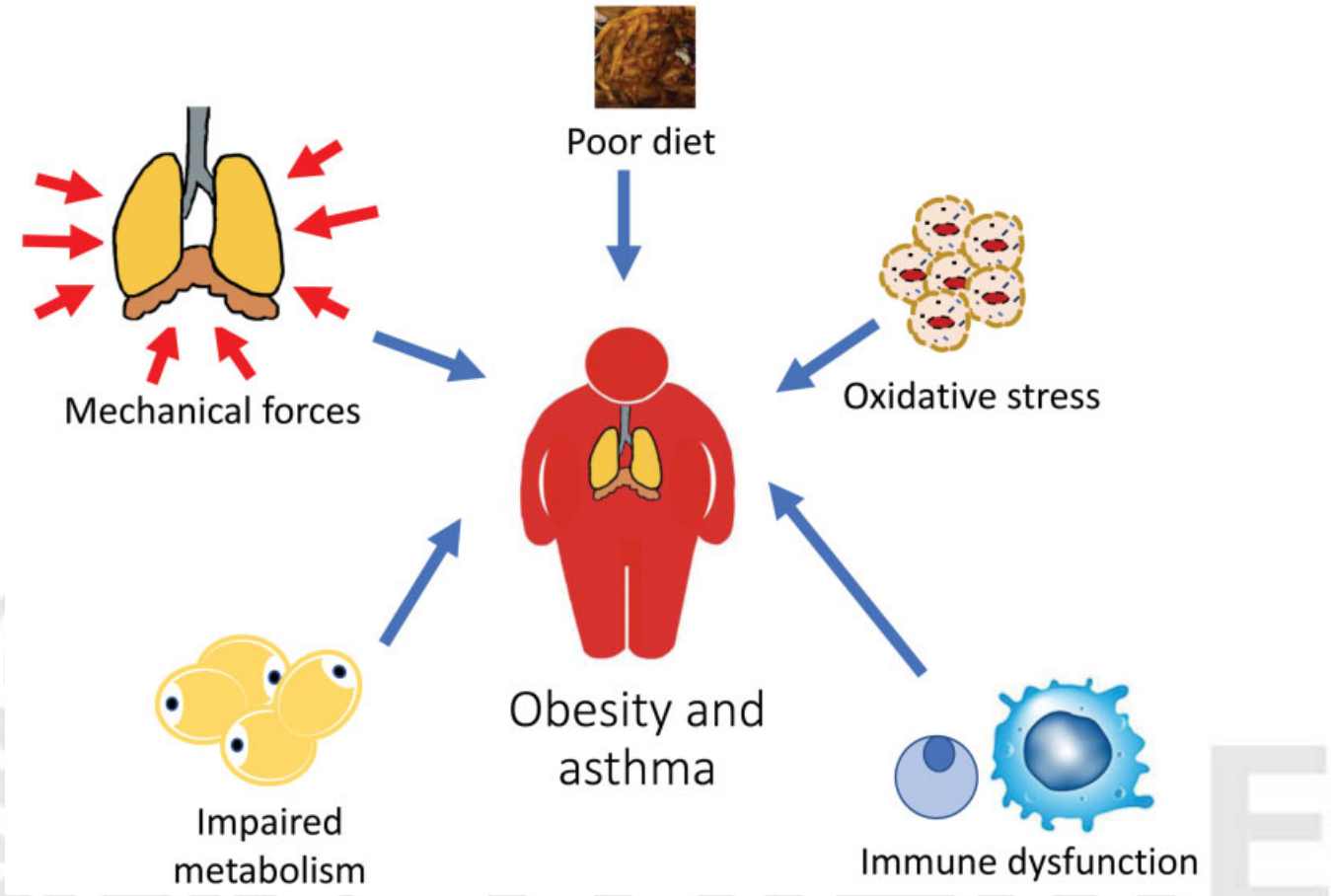

Fig. 1 Factors contributing to the pathogenesis of obesity and asthma.

mechanics: the restrictive effects of adipose tissue weigh down the thoracic cavity. However it is also related to metabolic changes, specifically insulin resistance: using data from 2007 to 2011 National Health and Nutrition Examination Survey (NHANES). Zhang and colleagues found that the relationship between decreased spirometric lung function was not related to markers of obesity (BMI or waist circumference) when controlled for insulin resistance in the general population, only in those in the highest tertile of insulin resistance; these data suggest that metabolic factors might have a very significant role in mediating the effects of adiposity on restrictive spirometry.[23]

Obesity is associated with expiratory dynamic airway collapse of the central airways, even in otherwise healthy people with obesity, which may also contribute to respiratory symptoms.[24] The reason for this central airway collapse is not known but may be related to loss of airway-parenchymal tethering in obesity. Obese individuals also breathe at lower lung volumes (measured as lower functional residual capacity and expiratory reserve volume), close to the closing volumes of the small airways. As a consequence of breathing at low lung volumes, they have a tendency toward airway closure during normal tidal breathing, which likely contributes to ventilation perfusion mismatch. All these changes occur in otherwise healthy people with obesity but who are not asthmatic. It is important to carefully evaluate airway physiology in people with obesity, understanding that there are multiple abnormalities that may cause respiratory symptoms that are not asthma.

The mechanical effects of obesity may contribute to some asthma-type physiology. Breathing at low lung volumes may elicit airway reactivity in otherwise healthy people,[25] however, improvements in airway reactivity with weight loss are not related to improvements in lung volume,[26] so it is unclear whether breathing at low lung volumes significantly contributes to airway reactivity in people with obesity and asthma.

Obese asthma often affects the small airways. Unfortunately, small airway function is not easily measured by routine pulmonary function tests. Obese asthma particularly manifests as increased peripheral lung stiffness, which can be measured with the oscillometry technique; this increased peripheral lung stiffness improves with weight loss.[26] The increased symptoms obese people develop during bronchoconstriction compared with lean people appears to be related to increased lung elastance (a measure of stiffness) which can also be measured by oscillometry.[27] Increased peripheral lung stiffness may be related to increased collapsibility of small airways, and reduced ability to recruit these collapsed airways: obese people with asthma have greater increases in resistance (measured by oscillometry)[28] and develop more air-trapping (visualized by CT) than obese controls simply during passive exhalation.[29] During bronchoconstriction

induced by methacholine, obese people with late onset non-allergic asthma develop persistent rapid shallow breathing (compared with lean asthma, and obese and lean controls), suggesting inability to recruit airways that collapsed during induced bronchoconstriction.[28] These physiologic changes of increased small airway closure likely also contribute to the increased closing index (fall in FVC/Fall in FEV_1) in obese people with asthma in response to methacholine.[30,31] For obese people with suspected asthma, not confirmed by conventional spirometric testing (with bronchodilator or challenge test), oscillometry may be a more sensitive indicator of distal airway dysfunction.

Oxidative Stress and Nitric Oxide

Oxidative stress is increased in the airways of people with obesity, though this may not be specific for asthma, as obese controls have higher levels of nasal lavage 8-isoprostanes than obese asthmatics, and 8-isoprostanes in people with asthma are inversely related to asthma control.[32] What may be more significant is the decreased level of fractional exhaled nitric oxide (FeNO) that is associated with increased airway oxidative stress. While FeNO is conventionally used as a marker of eosinophilic airway inflammation in asthma, nitric oxide (NO) is an endogenous bronchodilator, and so decreased levels may worsen bronchoconstriction: a recent pilot study using supplementation with citrulline to increase endogenous NO in obese people with asthma and low FeNO, found improvements in lung function and asthma control associated with increases in FeNO.[33] Oxidative stress, perhaps through effects on the endogenous bronchodilator NO, may contribute to the pathophysiology of obese asthma (►**Fig. 1**).

Type 2 Inflammation

Routine measures of type 2 airway inflammation (exhaled NO, sputum eosinophils, and circulating eosinophils) are altered in obese people with asthma.[34] Sputum eosinophils do not correlate with airway wall eosinophils in obese asthma: Desai et al showed that submucosal eosinophilia was increased in people with obesity, and did not correlate with sputum eosinophils (which were similar in lean and obese subjects).[35] Trafficking of eosinophils to the lung from blood may also be altered: obese people have increased uptake of radiolabeled circulating eosinophils into the lung measured by single photon emission computed tomography compared with lean people with asthma.[36] These findings in people are mirrored by studies in mice models of allergic asthma: airway wall eosinophils are increased in obese animals, while bronchoalveolar lavage eosinophils are higher in lean animals.[37] In aggregate, the data suggest changes in eosinophil trafficking to the airway lumen in people with obesity, and that conventional markers of type 2 airway inflammation may not always detect type 2 airway inflammation in obese people with asthma (►**Fig. 1**).

Metabolic Inflammation

Asthma in people with obesity is associated with increased markers of adipose tissue inflammation compared with obese people without asthma.[20,38] In people with asthma, increased circulating levels of interleukin 6 (a pro-inflammatory mediator produced by adipose tissue) correlate with asthma severity, suggesting that metabolic dysfunction of adipose tissue may contribute to asthma severity (even among non-obese people).[39] One metabolic mediator that is showing promise as a target for obese asthma is glucagon-like peptide receptor-1 (GLPR-1); GLPR-1 agonists are currently used to treat type-2 diabetes mellitus. GLPR-1 agonists have shown promise in preclinical mouse models of obese asthma,[40] and people with obesity and asthma prescribed GLPR-1 agonists for diabetes had significantly fewer asthma exacerbations than those prescribed other medications for diabetes.[41] There are also data supporting metformin having efficacy in people with both asthma and type 2 diabetes.[42] Emerging data suggest that metabolic dysfunction of adipose tissue may contribute to asthma in people with obesity, and data from animal models and epidemiological studies suggest that targeting metabolic dysfunction may have efficacy for the treatment of obese asthma (►**Fig. 1**).

Infections

The COVID-19 pandemic has clearly shown that obese people are at increased risk of severe disease related to respiratory viral infections.[43] There are also data suggesting that obese people have increased risk of severe disease related to influenza[44] and respiratory syncytial virus.[45] Obesity significantly increases the requirement for mechanical ventilation and the duration of stay in the intensive care unit for influenza-infected patients.[46,47] Furthermore, individuals with obesity exhibit higher influenza viral loads, shed virus for longer and harbor the emergence of more highly pathogenic viral variants than lean patients.[47,48] Adults with obesity and asthma have an increased risk of severe symptoms when they develop a respiratory tract infection compared with lean people with asthma.[49] There are likely many reasons that people with obesity might have more severe disease related to infections, given the profound effects that obesity can have on immune responses that are critical for airway host defense. For example, Peters et al published that gene markers of CD8 T cell function in sputum decrease in proportion to BMI, suggesting that cell-mediated immunity critical for responding to airway viral infection is decreased in obesity.[50] The clinical implications of increased severity of viral infections in obese people with asthma are not yet clear: we do not yet have different recommendations for treating infections in lean and obese asthma. The recognition that obese people are one of the risk groups of COVID-19, and so need to be prioritized for vaccination, may have lessons for the care of people with obesity and asthma.

Diagnosis of Asthma in the Obese Patient

Asthma is diagnosed by history, physical examination, and symptom burden. Patients with allergic asthma often present with nasal irritation and swelling due to comorbid allergic rhinitis, whereas patients experiencing respiratory distress can demonstrate expiratory wheezing and a prolonged expiratory phase. Laboratory examination is often

unremarkable; however, peripheral eosinophilia and/or an elevated IgE and/or fraction of expired NO can be elevated in subsets of asthmatics.

Assessing airway inflammation can be a useful adjunctive test for the diagnosis of asthma, and valuable for directing treatment of asthma. Unfortunately, Type 2 inflammation can be difficult to assess in the obese patient as conventional biomarkers of inflammation (blood eosinophil counts, fraction of exhaled NO, IgE levels and sputum eosinophils) appear to be modified by obesity, as noted above. Lugogo et al performed secondary analyses of 652 subjects enrolled in the Asthma Clinical Research Network trials and found that these biomarkers are poorly predictive of eosinophilic airway inflammation in the obese patient with co-morbid asthma and suggested that lower cut points for peripheral eosinophils (96 cells/uL), IgE (268 IU), and FeNO (14.5 ppb) be used.[34] We suggest that obese patients may require very careful evaluation for Type 2 airway inflammation, with different thresholds than those used in lean people.

Most diagnoses of asthma are made clinically without confirmation by physiologic lung function testing.[51] A reduced forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) on spirometry coupled with bronchodilator reversibility or heightened sensitivity to methacholine or histamine on airway challenge can provide objective evidence to increase the specificity for diagnosing asthma. However, in people with obesity, spirometry does not detect changes in peripheral airways, often the site of dysfunction in obese asthma; testing incorporating oscillometry might be appropriate. Unfortunately, many of these tests are often not routinely available in clinical practice.

Obese patients with respiratory symptoms present a challenge to the health care provider. The effects of weight on respiratory mechanics can cause breathlessness resulting in overdiagnosis of asthma and inappropriate use of medications with increased risk of side effects.[16,51,52] Obesity can also result in underdiagnosis and undertreatment of asthma, as symptoms may be attributed to weight and/or perception bias.[51] In total, asthma is misdiagnosed in approximately 30% patients.[52] These concerns emphasize the need for physiologic lung function testing in this patient population.

Effect of Obesity on Asthma Control and Response to Medication

Obesity is increasingly recognized as contributing to severe and difficult to control asthma. Obesity is also associated with reduced lung function[53] and worse asthma outcomes, including increased use of short acting bronchodilators and corticosteroids, emergency room visits,[54–56] and asthma-related hospitalizations.[55] Indeed obesity is a significant risk factor for severe asthma exacerbations requiring mechanical ventilation.[56] Therefore it is not surprising that obese patients report worse quality of life compared with non-obese asthmatics.[57]

One reason for poor control and increased severity may be that response to asthma medications is influenced by obesity.[54,58–61] Current treatment recommendations are tailored to reducing a patient's level of risk and impairment, and focus on use of ICS used alone or in combination with short and long-acting β agonists, muscarinic antagonists, and leukotriene receptor antagonists. The NAEPP guidelines and GINA report do not differentiate selection or dosing of pharmacotherapy for asthma patients with obesity,[62,63] yet an increasing number of studies demonstrate poor response to conventional asthma therapy in the obese patient. Work by Peters-Golden in 2006 was the first to show that BMI influenced response to asthma medications: the response to ICS was reduced in obesity, response to leukotriene antagonists was similar, and the placebo response was lower suggesting that BMI may influence the natural course of asthma control.[58] Similar findings of reduced efficacy of asthma medications by obesity have been reported with use of ICS and ICS/LABA combinations,[59–61,64] theophylline,[65] and oral steroids.[60] These details are outlined in ►**Table 2**.

The effectiveness of biologics in the management of the obese asthma patient is controversial. Newer biological therapies including anti-IgE agents such as omalizumab, anti-interleukin-5 (IL-5), or IL-5 receptor agents, such as reslizumab, mepolizumab, benralizumab, and anti-IL4/IL-13 agents such as dupilumab are effective in reducing exacerbations and improving asthma control in eosinophilic asthma.[61,64,66,67] However, data are conflicting regarding efficacy of biologics in obese patients with asthma.[68–71] While work by Gu et al reported improvement in asthma control in obese and lean patients on omalizumab, the improvement was blunted as BMI increased, and lung function (FEV_1 and FVC) improved in lean but not obese people on omalizumab.[68] Similar findings were reported by Sposato et al in a retrospective review of 340 patients with moderate to severe asthma where obesity reduced response to FEV1, FVC, and asthma control on omalizumab.[70] In contrast, work by Oliveira et al showed a greater impact of omalizumab in obese patients. After 12 months of omalizumab, FEV1 improved in obese but not non-obese patients with asthma. The reduction in FEV1 was associated with a $<5\%$ reduction in BMI as well as decreased corticosteroid use.[72]

Therapies targeted at IL-5 and the IL-5 receptor have also produced conflicting results as outlined in ►**Table 3**. In a supervised cluster analysis of the DREAM study, obese patients with elevated eosinophils and higher airway reversibility were found to benefit the most from mepolizumab and experienced a greater reduction in exacerbations than non-obese patients.[69] Although mepolizumab was also shown to reduce exacerbation rate, increase FEV_1, and improve asthma control in a small cohort of patients with severe asthma regardless of obesity,[73] in a large meta-analysis of the phase 3 MENSA and MUSCA studies,[74] annual exacerbation rate was decreased but lung function was not significantly improved in the obese group. Similar findings were seen in a pooled analysis of the SIROCCO and CALIMA phase 3 trials.[71] However, benralizumab was less effective in reducing the annual exacerbation rate in patients with BMI 35 kg/m^2. Although reslizumab uses weight-based dosing regimens, studies examining efficacy of reslizumab by BMI have not been reported.

Table 2 Effect of obesity on clinical response to conventional asthma medication

Author	Population	Intervention	*n*	Groups	Outcomes
Peters-Golden et al 2006[58]	Adults	Montelukast vs. beclomethasone vs. placebo	3,073	Lean vs. obese asthma	Less improvement in asthma control days with ICS with increasing BMI; No change with montelukast
Dixon et al 2006[65]	Adults	Theophylline vs. montelukast vs. placebo	448 (228 obese)	Lean vs. overweight vs. obese asthma	Increased asthma exacerbation risk in obese subjects with theophylline; no change with montelukast
Boulet and Franssen 2007[59]	Adults	Fluticasone vs. fluticasone-salmeterol	1,242	BMI <20, BMI 20–24.9, BMI 25–29.9, BMI 30–34.9, BMI 35–39.9, BMI ≥40 kg/m^2	Less improvement with asthma control with ICS and ICS-LABA with increasing BMI
Sutherland et al 2008[60]	Adults	Dexamethasone	33 asthma; 12 non-asthma	Obese + overweight vs. lean asthma vs. non asthma	Decreased in vitro response to dexamethasone in overweight and obese patients with asthma
Sutherland et al 2009[105]	Adults	ICS vs. ICS-LABA	1,265	BMI <25 kg/m^2 vs. BMI ≥25 kg/m^2	Decreased FEV1 and change in FeNO in obese patients on ICS containing medications
Camargo et al 2010[106]	Adults	Fluticasone vs. fluticasone-salmeterol	475 (207 obese)	BMI <20, BMI 20–24.9, BMI 25–29.9, BMI 30–34.9, BMI 35–39.9, BMI ≥40 kg/m^2	In African Americans, BMI ≥40 was associated with an attenuated evening peak flow and an increased rate of asthma exacerbations
Forno et al 2011[107]	Children	Budesonide vs. nedocromil/ placebo	1,027 (322 overweight/obese)	Non-overweight vs. overweight/obese asthma	Overweight/obese children showed a decreased response to ICS on measures of lung function and ER visits/hospitalizations for asthma
McGarry et al 2015[108]	Children	ICS/LABA	2,963	Obese (BMI ≥95 percentile) versus non-obese (BMI <95 percentile)	Bronchodilator unresponsiveness is higher among obese Black and Hispanic children and adolescents compared with non-obese
Khurana et al 2019[109]	Adults	Tiotropium as add-on therapy to ICS vs. placebo	55	BMI <18.5, BMI 18.5 <24.99, BMI 25–29.99, BMI ≥30 kg/m^2	Peak FEV1; trough FEV1; Tiotropium reduces FEV1 independent of BMI

Abbreviations: BMI, body mass index; FEV, forced expiratory volume; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

Table 3 Effect of obesity on clinical response to biologics in the treatment of asthma

Author	Population	Intervention	*n*	Groups	Outcomes
Ortega et al 2014[69]	Adults	Mepolizumab	616 (102 obese)	Cluster 1–4 of DREAM	Elevated eosinophils and higher airway reversibility in obese asthma had a higher exacerbation reduction with mepolizumab than in non-obese with asthma
Sposato et al 2018[70]	Adults	Omalizumab	340	Lean vs. obese asthma	Obesity reduces effectiveness of omalizumab (FEV1%, FVC%, ACT lower in obese)
FitzGerald et al 2018[71]	Children and adults	Benralizumab	2,295	BMI $\leq$35 kg/m^2; BMI $>$35 kg/m^2	Benralizumab is less effective in reducing the annual exacerbation rate in patients with BMI $>$35 kg/m^2
Oliveira et al 2019[72]	Adults	Omalizumab	32 (19 obese)	BMI $<$30 kg/m^2; BMI $\geq$30 kg/m^2	Omalizumab improved ACT score and FEV1, and reduced BMI and asthma exacerbations over a 12-mo time period
Albers et al 2019[74]	Adults	Mepolizumab	995 (268 obese)	BMI $<$25 kg/m^2; BMI 25–30 kg/m^2; BMI $\geq$30 kg/m^2	Mepolizumab reduced annual clinically significant exacerbation rates for all BMI categories but did not improve lung function in the obese group compared with placebo.
Gu et al 2020[68]	Adults	Omalizumab	45 (19 obese)	Obese vs. non-obese	As BMI increased lung function (FEV1% predicted and FVC % predicted) and asthma control (ACT score) decreased in patients treated with omalizumab
Crimi et al 2020[73]	Adults	Mepolizumab	31 (11 obese)	Severe asthma with comorbidities (obesity, gastroesophageal reflux disease, allergy, non-allergic rhinitis with eosinophilia, bronchiectasis, nasal polyps)	Mepolizumab was effective in severe asthma in reducing exacerbations, increasing FEV1, increasing ACT and decreasing peripheral eosinophils regardless of the presence of comorbidities.

It is not surprising that obese asthma patients have a differential response to asthma medications. Most of the approved therapies for asthma were studied using lean animal models and tested in leaner patients than those now encountered in clinical practice. Results of prior clinical trials may not be as relevant as our population continues to become more obese. Moreover, since obese patients with late-onset asthma[75] usually lack eosinophilia and often have a neutrophilic phenotype, new therapies for type 2 low asthma in the obese are needed. As of now, therapies treating obese asthma follow the same guidelines and recommendations for lean asthma.

Treatment of Co-morbidities

Obese patients with asthma frequently have an increased prevalence of co-morbidities that could adversely affect airway disease. Depression is increased in people with obesity and has been associated with poor asthma control.[76] Although there are no studies clearly showing that treatment

of depression improves asthma control, depression is a co-morbidity that should arguably be treated anyway, irrespective of co-morbid asthma. Similarly, gastro-esophageal reflux disease is increased in people with obesity: while treating mild GERD does not improve asthma control,[77] significant GERD should be treated for its own sake. Finally, obese people have a high risk of having obstructive sleep apnea. Sleep apnea has been associated with poor asthma control,[78] and is a co-morbidity that requires intervention; it seems reasonable to screen for and treat obstructive sleep apnea in obese patients, as it is likely to improve nocturnal symptoms.

Dietary Interventions

As obesity is associated with poor asthma control, one obvious intervention to consider for treating obesity-related asthma is weight loss. There have been several studies—most small, single center studies—that have addressed diet and behavioral interventions to promote weight loss in asthma, and one that used both a dietary and medication intervention.[79–87] These are summarized in ►**Table 4**. In balance, these studies suggest that significant weight loss is associated with improvement in asthma control. The largest study, by Ma et al, did not find a significant difference between groups when comparing the weight loss intervention with the control group, but found that those who lost ≥ 5% weight had a statistically significant improvement in asthma control, and those who lost ≥10% weight had a clinically and statistically significant improvement in asthma control.[84] Other studies have found that at least 5% weight loss is required to achieve significant improvements in asthma control.[81] Some studies have assessed the role of exercise as an adjunct to dietary intervention: Scott et al did not find that exercise significantly improved outcomes compared with the dietary intervention alone (both diet and diet with exercise groups lost a similar amount of weight),[81] whereas Freitas et al found that exercise combined with dietary intervention improved asthma control compared with dietary intervention alone (the exercise group did lose slightly more weight in this latter study).[85] There is only one study addressing weight loss in children, which also found improvements in asthma control with weight loss.[82] Overall these studies suggest that 5 to 10% weight loss can produce improvements in asthma control, and exercise combined with dietary intervention may be beneficial.

There has been one study of a pulmonary rehabilitation exercise intervention, which included nutritional counseling and psychological group sessions, for obese patients with asthma; 25 participants that received the pulmonary rehabilitation intervention had improvements in asthma control, and reduction in weight was greatest in the 11 participants that received pulmonary rehabilitation combined with an internet based self-management support program.[88] However, exercise interventions might be challenging for people suffering with asthma and obesity. Our own group has found that patients with obesity and asthma, which frequently affects minority populations, were associated with marked impairments in quality of life related to physical health, and low levels of physical activity,[89] suggesting that weight loss interventions that include significant exercise component will likely need to be tailored for people with marked impairments in physical health.[90]

Short of weight loss, focusing on dietary quality may be another strategy to improve asthma control. Wood et al showed that a meal high in saturated fatty acids upregulated IL1β and TLR4 in non-obese asthmatics, though they did not see a significant effect in obese asthmatics.[91] The same group have previously shown that a high fat meal reduces bronchodilator responsiveness,[92] and that soluble fiber can affect bronchodilator responsiveness and airway inflammation.[93] These data suggest that it is not just the contribution of poor diet to weight gain, but the composition of the diet itself which could impact asthma control. There have been a few clinical trials addressing dietary quality interventions to treat asthma: Wood et al compared a low versus high antioxidant diet, and found decreased risk of exacerbation in the high antioxidant diet (among 46 subjects who increased their fruit and vegetable intake); of those on the low antioxidant diet, half received an anti-oxidant supplement, and this did not improve outcomes, suggesting the whole food component of the intervention was the important feature.[94] Berthon et al enrolled 68 children who had been eating a diet low in fruit and vegetables, and randomized them to a high fruit and vegetable diet versus control, though they did not detect a significant effect on asthma exacerbations, they detected improvements in lung function by oscillometry in the intervention group.[95] Ma et al randomized 90 adults with a low quality diet to the DASH diet (Dietary Approaches to Stop Hypertension) versus control for 6 months, and observed a trend to improvement in asthma control in those on the DASH diet.[96] Sexton et al enrolled 38 adults into a high versus low Mediterranean diet intervention, and found trends toward improvements in spirometry and asthma quality of life with the intervention.[97] Together these data support the need for studying improving dietary quality as a potential treatment option for people with poorly controlled asthma and obesity, though larger multicenter studies are needed before firm recommendations can be made.

Bariatric Surgery

There have been several studies of people with asthma undergoing bariatric surgery. These studies report significant improvements in asthma control and quality of life,[98,99] decreased asthma medication use,[100] and improvements in airway reactivity (particularly in those with late onset non-allergic asthma).[101] Hasegawa et al reported among 2,261 obese patients with asthma aged 18 to 54 years who underwent bariatric surgery identified using a population-based emergency department and inpatient sample in three states (California, Florida, and Nebraska), a significant reduction in asthma exacerbations (OR 0.42) after surgery compared with before surgery.[102]

Forno et al reported that those asthmatics with metabolic syndrome had lesser improvements in asthma control

Table 4 Results of lifestyle weight loss interventions for people with obesity and asthma

Author	Population	Intervention	*n*	Weight outcomes	Asthma outcomes
Stenius-Anniala et al 2000	Adults	Very low energy diet versus control	28	14.5 vs. 0.3% weight loss	Intervention group had improvement in peak flow, symptoms, reduced exacerbations
Johnson et al 2007	Adults	Alternate day caloric restriction	10	8% weight loss in nine adherent participants	Significant improvements in asthma control and quality of life
Scott et al 2013	Adults	Diet, vs. diet and exercise vs. exercise	46	8.5 vs. 8.3 vs. 1.8% weight loss	Asthma control improved in diet and diet and exercise group; 5–10% weight loss produced clinically significant improvements in asthma control
Jensen et al 2013	Children (aged 8–17)	Diet vs. wait list control	28	BMI *z*-score decrease in diet group	Significant improvement in asthma control in diet group only
Dias-Júnior et al 2014	Adults	Weight loss program (diet + sibutramine [10 mg/d] + Orlistat [≤120 mg/d]) vs. control	33 (22 on weight loss program)	7.5% vs. 0	Significant improvement in asthma control in weight loss group only, also improvement in FVC
Ma et al 2015	Adults	Diet vs. usual care	330	5 vs. 1.3% in diet vs. usual care	No difference in asthma control overall, though those who lost ≥5% weight had improvements
Pakhale et al 2015	Adults	Behavioral weight loss intervention vs. control	22 (16 assigned to weight loss)	15% weight loss in intervention group	Improved airway reactivity, asthma control, asthma quality of life and lung function in weight loss intervention group only
Freitas et al 2017	Adults	Diet, versus diet and exercise	55	3.3 vs. 6.7% weight loss in group with diet, vs. diet and exercise	Significant improvements in asthma control in diet and exercise group only, greater improvement in asthma-related quality of life
Özbey et al 2020	Adults	Dietary restriction versus control	55	6.1% in diet group vs. 0.1% in control group	Intervention group had improved asthma control, asthma quality of life, FEV_1, and FVC

Abbreviations: FEV, forced expiratory volume; FVC, forced vital capacity.

following bariatric surgery than those without metabolic syndrome, suggesting that metabolic dysfunction may lead to persistent airway dysfunction in people with obesity and asthma.[103] Studies addressing how the pathophysiology of asthma is altered by weight loss have found that asthma control is particularly associated with improvements in small airway function,[26,104] and von-Huisstede reported a decrease in airway wall mast cells.[104] Overall these studies

suggest that bariatric surgery can lead to significant improvements in asthma control, and decreased exacerbations associated with changes in airway pathophysiology, though people with pre-existing metabolic dysfunction may not experience such marked improvements, and those with allergic asthma are likely to have persistent airway reactivity.

Summary/Conclusion

Over the past 20 years, the relationship between obesity and asthma has emerged as a major public health issue, with the majority of people with severe asthma in the United States now obese. This leads to significant diagnostic challenges: distinguishing normal symptoms of obesity from those of asthma can be challenging and may require sophisticated physiological testing to detect changes in the periphery of the lung. Changes in immune function may modify the presentation of type 2 inflammation in asthma and increase susceptibility to severe viral infections. Metabolic dysfunction and oxidative stress may contribute to novel forms of airway disease. Treatment of such patients can be challenging, as response to medications is altered. Co-morbidities may also contribute to poor asthma control. Consideration of diet and lifestyle interventions can be particularly helpful yet may be particularly challenging for clinicians to implement. Finally, bariatric surgery may have a role in some patients, particularly those with multiple co-morbidities, though this needs to be weighed against the potential increased risk of morbidity in those with underlying airway disease.

Conflict Of Interest
None declared.

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