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ASTHMA (V ORTEGA, SECTION EDITOR)

The Effects of Obesity in Asthma

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Abstract

Purpose of Review Rising costs and increasing morbidity makes the identification and treatment of high-risk asthma phenotypes important. In this review, we outline the complex relationship between obesity and asthma.

Recent Findings Studies have confirmed a bi-directional relationship between obesity and asthma. Pathophysiological factors implicated include genetic risk, the effect of diet and microbiome, and obesity-related cytokines. There have been robust, albeit derived, efforts to phenotype this group with distinct clinical presentations based on age of onset of asthma. Unfortunately, the poor performance of biomarkers and traditional lung function testing has impeded diagnosis, phenotyping, and management of the obese asthma patient. There is also a lack of targeted interventions with weight loss showing some benefits.

Summary Obesity increases the prevalence of asthma and is associated with worse outcomes. There are unique research and clinical challenges while managing this group of patients.

Keywords Obesity · Asthma · Management · Biologics · Severe

Introduction

The World Health Organization (WHO) defines overweight and obesity as abnormal and excessive fat accumulation that may impair health [1]. Rapid urbanization and globalization have resulted in a pandemic of obesity in developed nations [2, 3]. The WHO estimates that over 1.4 billion adults older than 20 years of age are overweight [1] and in the USA, a third of the adult population is now considered to be obese [4, 5•]. Having a body mass index (BMI) ≥25 (overweight) or ≥30 (obesity) is associated with increased risk of cardiovascular disease, diabetes, osteoarthritis, and various malignancies [6–8].

It is unclear if obesity increases the risk of developing asthma or vice versa; however, there is evidence that they are closely related and significantly impact each other's natural progression [9•, 10]. Multiple studies have shown that obesity is associated with an increased risk of developing asthma in a dose-dependent manner in adults [11••, 12–15] and children [16, 17]. The strongest predictor of developing asthma later in childhood is a rapid increase in body weight in the first 2 years of life [18]. In adults, the prevalence of asthma is 2–3% higher in obese compared to overweight or normal weight individuals [19]. Women have a higher prevalence of asthma, and the impact of obesity appears to be more profound in this population as well with 6–7% higher prevalence when compared to normal weight women [19]. Finally, it is important to note that the prevalence of obesity is 11–12% higher in adult asthmatics compared to non-asthmatics [20] and up to 60% of severe asthma patients are obese [21]. One possible explanation for this finding is that poor quality of life and exercise intolerance associated with asthma leads to more obesity.

Asthma is an economically devastating disease in the USA, estimated to cost approximately $82 billion annually [22]. The economic cost, overall morbidity, and lack of significant progression in treatment or diagnosis makes researching the obesity-asthma interaction of paramount importance. In this review, we will summarize the latest available literature on this topic and emphasize the gaps needed to be filled by future research.

Pathophysiology

Asthma in the obese may represent a clinical phenotype as further discussed below, but the underlying pathophysiology

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of this state appears to be quite diverse with multiple mechanisms and overlapping modulators (see Fig. 1). We will summarize some of the key data below.

An Inflammatory State

Obesity is a metabolically active inflammatory state where increased levels of macrophages, leptin, adiponectin, interleukin (IL)-1β, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α along with other pro-inflammatory markers are released by adipose tissue and believed to contribute to the metabolic syndrome associated with cardiovascular disease and insulin resistance [23, 24•]. Leptin in particular has been studied as an individual contributor, and a mouse study found that leptin infusion leads to higher levels of airway hyperreactivity (AHR) and serum immunoglobulin E (IgE) but has never been studied as specific target in asthma [25].

Some argue that metabolic syndrome is the true culprit of worsening asthma. An observational study found that patients with metabolic syndrome experienced higher rates of poor asthma control following bariatric surgery compared to patients without metabolic syndrome, suggesting that the presence or absence of metabolic syndrome is more important than the effect of weight loss [26•]. Complex mutual interactions of obesity with systemic non-atopic inflammation have been found to produce T helper (Th)1 polarization, monocyte activation, and metabolic dysregulation via insulin resistance and dyslipidemia [27, 28]. These studies suggest that contemporary asthma management may be more effective if metabolic syndrome were aggressively treated.

More recently, innate lymphoid cells (ILCs) have been noted to play an important inflammatory role in asthma. Group 2 ILCs produce type 2 cytokines, including IL-5 and IL-13, both of which have been heavily studied as therapeutic asthma targets with divergent results. A murine model demonstrated that obese mice exposed to ozone had higher levels of lung IL-13-producing ILC2 cells than their lean counterparts [29]. The conflicting phase 3 trials of lebrikizumab (anti-IL13 monoclonal antibody) in asthma that led to abandonment of further development may have had more distinct results in an obese asthma population and represent a potential target population that is supported by translational models.

Oxidative stress may be handled differently in obese asthmatics that contributes to a hyperinflammatory state. Obese patients with late-onset asthma in the Severe Asthma Research Program (SARP) who had decreased L-arginine to asymmetric dimethyl arginine (ADMA) ratios were noted to have increased respiratory symptoms, reduced lung function, lower IgE levels, and reduced fractional exhaled nitric oxide (FeNO) [30]. Murine models have shown that lower L-arginine to ADMA ratios can lead to nitric oxide synthase uncoupling and increased airway oxidative stress [31]. When human bronchial epithelial cells were obtained via bronchoscopy and placed in reduced L-arginine media conditions, treatment with L-citrulline restored nitric oxide formation. These studies show that oxidative stress is not processed equally in obese patients with asthma and suggest a potential therapeutic opportunity with an amino acid [32].

In summary, these studies show that obesity affects airway inflammation through a combination of pathways [23–25]. These include cytokine over-production from adipose tissue, consequences of metabolic syndrome, the presence of higher levels of pro-inflammatory ILC2, and increased pathologic response to oxidative stress. The immense variety of inflammatory cytokines and processes that seem to occur simultaneously in this population may explain the poor response to therapy when simply one cytokine, antibody, or receptor is targeted.

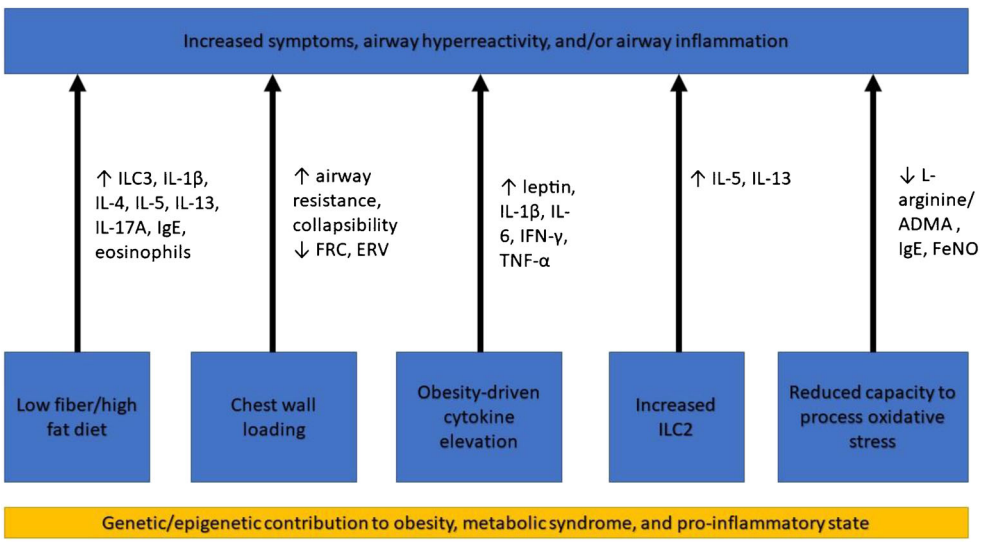

Fig. 1 The contribution of various obesity-related mechanisms to pathology of asthma

Anatomical Considerations

Differences in pulmonary mechanics may contribute to respiratory symptoms in obese asthmatics. Obesity reduces most lung volumes through increased chest wall loading with the most profound impact on functional residual capacity (FRC) and expiratory reserve volume [33]. Decreased FRC is directly related to airway resistance and inversely with airway conductance seen in obstructive lung disease [34]. Modeling of respiratory system impedance suggests that late-onset obese asthma is characterized by excessive collapsibility of the small airways [35]. Increased airway resistance and closing of bronchioles can lead to symptoms of dyspnea, wheezing, and cough. As such, non-pharmacologic interventions to improve mechanics could help to relieve symptoms in obese patients with asthma such as weight loss for chest wall offloading or positive pressure ventilation to limit bronchiole closure.

Genetics and Epigenomics

A variety of genetic mechanisms linking obesity and asthma have come to light in recent years [36•] with several studies demonstrating single nucleotide polymorphisms (SNPs) associated with BMI in subjects with asthma [10]. These loci, however, do not fully explain the association between obesity and asthma, and epigenetic influences via circulating microRNAs that can modify gene expression are increasingly being recognized [36•]. More recent studies are investigating genomic approaches in combination with environmental factors to better understand the complex relationship between obesity and asthma though research in this area is far from complete [37]. Thus, while a family history of asthma may increase the risk of development in an individual, the inheritance pattern is complex and unpredictable.

Diet and Microbiome

There is growing interest in the role of diet on the pathophysiology of asthma through direct effects on the airway or indirectly via inflammation and alterations in the gut microbiota. Specifically, fat, fructose, and fiber have been found to play key roles in murine studies. Mice that were fed a high fat or high fructose diet developed typical signs of asthma including increased airway resistance and AHR [38]. A high-fat diet was also associated with increased production of IL-1 β, IL-17-producing group 3 ILCs, and the expression of the pro-inflammatory NLRP3 gene mRNA in the lungs [39]. These studies suggest that diet can influence inflammation and possibly produce clinically relevant endpoints in the form of increased AHR. Subsequent testing showed that blocking IL-1β signaling with IL-1 receptor antagonist anakinra decreased ILC3s and AHR in the obese murine model which could have implications in human subjects and has yet to be studied in a therapeutic context in asthma [39].

Low dietary fiber content has been associated with increased allergic airway inflammation in murine models. Mice fed low-fiber diets exhibited increased levels of eosinophils; lymphocytes and concentrations of IL-4, IL-5, IL-13, IL-17A; and total IgE while a high-fiber diet resulted in modified gut bacterial communities that showed an increase in anti-inflammatory short-chain fatty acids [40]. While dietary interventions have been scantly studied in obese asthmatics, one could postulate that the anti-inflammatory benefits seen in mouse models from increased fiber and decreased fat intake could have potential benefits in humans with relatively low risk, though how changes in the gut microbiome mechanistically alter the lung microbiome is currently under study.

Clinical Features and Phenotypes

Albeit more severe, those with obese asthma have the same constellation of symptoms as their lean counterparts such as dyspnea, wheezing, cough, nocturnal awakenings, and chest tightness. It is important to remember that a single symptom alone may be a poor indicator for disease severity or control. For example, dyspnea may be exaggerated in these patients at baseline as obese otherwise healthy patients, particularly women, have other mechanisms that drive their symptomatology such as increased cost of breathing [41] or perceptional issues [42]. When assessed globally, two clinical aspects appear to be clear about the effect of obesity on asthma—obesity worsens severity and control of asthma and the obese asthmatic is a distinct phenotype.

In adults, symptom burden of asthma is significantly higher in obese compared to non-obese asthmatics [43–45]. Obese patients tend to have higher rates of daily symptoms [44, 45] restricted activity days [44], missed work days, and a higher likelihood of being diagnosed with severe asthma [45]. Even after adjusting for variables such as smoking, gastroesophageal reflux (GERD), and steroid exposure, obese asthmatics tend to have a worse quality of life, asthma control, and more asthma-related hospitalizations [43]. Obese patients have been found to use more asthma medications including maintenance and burst oral corticosteroids (OCS) and daily short-acting β2 agonists (SABA) [45, 46]. Unfortunately, despite this higher use, there is a growing body of literature that also shows that these patients also have diminished responses to therapy [47–49]. Obese asthma patients are less likely to achieve control with an inhaler than non-obese patients [47, 50], and a large post hoc analysis found that the response of subjects to inhaled corticosteroid (ICS) and placebo was lower in obese compared to non-obese patients [48]. A possible explanation for the poor ICS response not addressed above could be increased production of obesity-related inflammatory cytokines

that reduce induction of mitogen-activated kinase phosphatase 1 by glucocorticoids [49].

As in adults, obesity has serious influences on pediatric asthma [10]. Children who are obese tend to have worse asthma control, quality of life, and more severe disease [51–55]. The poor response to therapy, seen in adults, has been replicated in pediatric asthma studies. Compared to non-obese children, obese and overweight children have a decreased response to ICS [56] and bronchodilators [57]. This has been associated with increased OCS exposure and more severe exacerbations [56]. A recent analysis of 38,679 children showed that obese asthmatics were more likely to have a 30-day readmission and a longer length of stay [53•].

Phenotypes are observable characteristics that result from the interactions of genotypes and the environment. Hierarchical cluster analysis of observable characteristics (symptoms, BMI, medication use, biomarkers, and exacerbation frequency) has allowed for meaningful phenotyping of the asthma population as a whole [58, 59]. The obese asthma phenotype was first revealed in the SARP as cluster 3 (late onset, obese, female, high sputum eosinophils, less atopic, sinus disease, frequent symptoms, and need for OCS) [58] and in the Leicester asthma study as cluster 2 (late onset, obese, female, low sputum eosinophils, high neutrophils, less atopic, and more frequent symptoms) [59]. There have been other attempts to phenotype the obese asthma patient as a stand-alone entity with a focus on asthma caused by obesity versus asthma complicated by obesity [10, 60••]; however, attempts to phenotype based on early versus late-onset asthma in obese patients have been more compelling [61–63]. There is convincing evidence that obese asthmatics with age of onset < 12 years tend to have atopic features, poor control, severe reduction in airway function with significant AHR, and elevated type 2 biomarkers (see below) with no sex predominance [61]. On the other hand, obese asthmatics with age of onset > 12 years tend to have less atopic features, less airway obstruction and AHR, better control, normal type 2 biomarkers, and female predominance [61, 63].

As with all asthmatics, it is important to assess co-morbid conditions in obese patients that can contribute to worse control. Obstructive sleep apnea (OSA) has been associated with poor asthma control [64] and in the SARP cohort was found to associate with increased asthma symptoms, rescue inhaler use, healthcare utilization, and worse quality of life [65]. Interestingly, OSA risk is also associated with increased neutrophilic inflammation which may be a possible driver of this inflammatory phenotype [65]. While it is universally accepted that obese asthma patients should be screened and then tested for OSA, the benefits of CPAP on asthma control has not been clearly demonstrated to date [66]. GERD is more prevalent in obese asthma patients though there is some conflicting data about its exact role in asthma control [64]. Similar trends are also seen in obese children [67]. While treatment of GERD has not been shown to convincingly improve asthma control [68, 69], most guidelines and expert opinions suggest that GERD should be controlled once it has been identified. Sinonasal disease was noted to be a part of the SARP cluster 3 phenotype [58] and may contribute to symptoms; however, a recent placebo-controlled study of nasal mometasone in 236 patients with poorly controlled asthma failed to show any major effects in lean or obese asthma patients despite the association between sinonasal disease symptoms with increased asthma severity [70].

Diagnostic Challenges

Obese asthmatics face additional barriers to diagnosis due to the confounding effect of obesity on various asthma surrogate measures. Critical management decisions rely on the successful categorization of a patient as type 2 or non-type 2 asthma which generally relies upon physical examination, responsiveness to corticosteroids, and objective data. There is concern however that commonly used diagnostic tests used to categorize lean asthmatics may not be accurate in the setting of obesity.

While peripheral eosinophil count, FeNO, and IgE have significant utility in lean asthmatics, their accuracy in obese asthmatics is questionable as an expanding body of data suggests that obesity attenuates these signals. A recent study using a validated surrogate gene expression signal for type 2 inflammation found that class III obesity in severe asthmatics diminished an otherwise strong correlation between type 2 inflammation and peripheral eosinophil count, raising concern that despite obese asthmatic may have high levels of type 2 inflammation but no elevation in eosinophils [71]. This mechanistic study validates what is seen clinically and has been observed in other studies, including a recent pooled secondary analysis of subjects involved in Asthma Clinical Research Network (ACRN) trials [72•, 73••]. Similarly, a large Swedish asthma study demonstrated that FeNO was decreased in symptomatic wheezing obese patients despite being elevated in similar lean patients [74] and a cross-sectional population cohort study from the Netherlands showed similar FeNO levels in obese and lean asthmatics despite increased wheezing and symptoms in the obese group [75]. This unfortunate suppression of nitric oxide generation in the lungs of obese asthmatics further confounds type 2 categorization attempts. Even in allergic asthma, IgE appears to be suppressed by obesity, as demonstrated by a British severe asthma registry [46] and a pooled analysis of ACRN trials [73••].

In addition, the detection of obstructive lung physiology is more challenging in obese patients. The effects of obesity on normal lung function have been well described previously [76] but can be briefly summarized as having a predominantly restrictive rather than obstructive effect on pulmonary function tests (PFTs). While the forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio is validated in

chronic obstructive pulmonary disease, there is much less consensus on its utility in asthma though it is still widely clinically used as a threshold for obstruction. However, due to the restrictive effect of obesity on PFTs, the FEV1/FVC ratio is not a reliable tool to screen for obstructive disease in the obese and has been shown to be preserved in obese asthmatics despite severe disease [77, 78].

AHR is, arguably, the closest thing to a gold standard in the diagnosis of asthma in the correct clinical context, yet it has been shown to inconsistently correlate in obese adult asthma [79]. Studies assessing the effect of obesity on AHR during methacholine challenge found a positive correlation except in patients that were diagnosed with asthma where there was no correlation noted [14, 80]. Seemingly in contrast to this finding, other studies in asthmatics have shown that increasing BMI has a positive correlation with airway closure (a potent contributor to AHR) during methacholine challenge as measured by %ΔFVC/%ΔFEV1 [81, 82]. This creates a clinically confusing scenario where patients with obese asthma are expected to have more airway closure and gas trapping, but this finding may not manifest as more severe AHR on a methacholine challenge test. Several small studies have assessed the effect of weight loss on AHR in obese adult asthmatics and have shown conflicting results, clouding the relationship even further [83–85]. The European Respiratory Society notes that the methacholine challenge is best used when pre-test probability for asthma is between 30 and 70% and is generally more useful when negative due to its high negative predictive value [86]. However, the data underlying cutoffs for a positive or negative test do not seem to account for obesity which, as demonstrated above, may adversely impact its accuracy [87].

While diagnostic tools for asthma are lacking in general, the negative impact obesity has on the sensitivity of our most reliable tests is significant. This is compounded by the more severe symptoms these patients tend to have that would allow them to qualify for targeted biologic therapies. This results in a conundrum where multiple tests may fail to diagnose a profoundly symptomatic patient with type 2 asthma, yet clinical suspicion remains high. It is our clinical experience that obese asthmatics must be approached in a multimodal fashion without excessive reliance on any single diagnostic test. In addition to the tests above, we also use responsiveness to corticosteroids or biologic therapies, exacerbation triggers, and physical exam findings (such as nasal polyps, urticaria, and wheezing) to diagnose and categorize obese asthmatics. There remains, however, significant work to be done to facilitate diagnosis in this challenging and symptomatic population.

Management

As discussed above, there are multiple unique hurdles for managing asthma in the obese patients. The general approach to these patients is similar to their non-obese counterparts despite extensive research on divergent outcomes in these populations (see Table 1 for a concise summary). Emphasis should be placed on inhaler technique, adherence, and weight loss. These patients should be managed with the usual inhaler-based asthma treatment steps with close monitoring for treatment failure, as observed in multiple studies [47–49, 57]. Monitoring of control should be multifaceted as conventional measures (such as biomarkers and pulmonary function tests) may be inaccurate and symptoms, such as dyspnea, maybe exaggerated even at baseline. Obese asthma patients should be screened for OSA, GERD, and sinonasal disease and treated appropriately, keeping in mind that treatment of these conditions has had mixed results on overall asthma control [64, 70].

It is important to understand the exact effects of weight loss. In a 2015 prospective, parallel-group study involving 22 asthmatics with a BMI ≥ 32.5, weight loss (achieved by a weight reduction program for 3 months) resulted in significant improvement in AHR, asthma control, lung function, and quality of life [83]. In a more recent 2017 paper, adding short-term exercise to a weight loss program (3 months) improved asthma control, lung function, and inflammatory markers of asthma [89•]. A 2019 systematic review involving four trials (246 children and 502 adults) concluded that weight loss from any measure (dietary restrictions, exercise or behavioral therapy) generally resulted in improved asthma control and quality of life [90]. Patients who fail a trial of conservative measures can be referred to bariatric surgery. It has been shown that bariatric surgery improves AHR [85], lung function, asthma severity, and control as well as asthma-related quality of life [91, 92•]. Two recent publications also showed that bariatric surgery improved the systemic and pulmonary inflammatory profile in these patients [93] as well as decreasing their asthma medications [94]. While these measures are being applied, it is important to quantify the degree of weight loss. Weight loss of ≥ 10% is usually required to produce meaningful improvement in asthma [88].

Direct data to support the role of targeted therapies, such as biologics, and non-conventional therapies, such as bronchial thermoplasty and chronic macrolide therapy, is lacking in the obese asthma patients. In some instances, obesity may reduce the responsiveness to therapies such as omalizumab [97•]. In other instances, obese patients may the most likely to benefit from certain therapies. In a supervised cluster analysis of the DREAM study [96], obese patients had a larger reduction in exacerbation rates than non-obese patients in response to mepolizumab (67% versus 35%) [95]. Studies to better characterize the obese asthma phenotype will drive development of targeted therapies and revolutionize how care is delivered to these patients.

Table 1 Studies evaluating factors influencing management of asthma in obesity

Management consideration	Study	Population /intervention	Key outcomes
Obesity is associated with poor response to asthma therapy	Peters-Golden 2006 [48]	• 3073 asthmatics • LTRA vs ICS vs placebo	•Placebo response for all end points was lower with increasing BMI
	Rodrigo 2007 [50]	• 426 asthmatics with severe exacerbations • Prospective ED cohort study	•Overweight/obese patients were hospitalized more frequently after initial ED albuterol therapy
	Boulet 2007 [47]	• 1242 asthmatics • ICS vs ICS + LABA	•Achieving well-controlled asthma is less likely with BMI ≥ 40
	Sutherland 2008 [49]	• 33 asthmatics • Dex-induced MKP-1 expression was studied	•Elevated BMI is associated with blunted in vitro response to dexamethasone
	Forno 2011 [56]	• 1027 asthmatic children • ICS vs placebo	•Overweight/ obese children showed decreased response to ICS in terms of lung function and ER visits/hospitalizations
	McGarry 2015 [57]	• 2963 asthmatic children • Case-control study data	• Obesity is associated with bronchodilator unresponsiveness among black and Latino children and adolescents
Effects of weight loss on asthma	Pakhale 2015 [83]	• 22 asthmatics, BMI ≥32.5 • Behavioral weight reduction program × 3 months	• Weight loss improved asthma severity, AHR, asthma control, lung function, and QoL
	Ma 2015 [88]	• 330 obese asthmatics • Pedometer, education, access to weight management clinic × 12 months	• Weight loss of ≥ 10% may be required to produce clinically meaningful improvement in asthma
	Freitas 2017 [89•]	• 55 obese asthmatics • Weight loss program plus exercise vs weight loss program plus sham × 3 months	• Adding exercise to a weight loss program improves asthma control, lung function, and anti-inflammatory biomarkers
	Okoniewski 2019 [90]	• Systematic review • Four RCT involving children ($n = 246$) and six RCT involving adults ($n = 502$)	• Weight loss generally results in improvement in asthma QoL and asthma control. Lung function improvements were noted more consistently in adults
Effect of bariatric surgery on asthma	Dixon 2011 [85]	• 23 asthmatics compared to control and baseline at 12 months after bariatric surgery	• Bariatric surgery results in improvement in asthma control and QoL. AHR improved in patients with normal serum IgE.
	Boulet 2012 [91]	• 12 asthmatics before, 6 and 12 months after bariatric surgery	• Bariatric surgery resulted in improvement in AHR, asthma severity, asthma medication need, and lung volumes.
	Maniscalco 2017 [92•]	• 26 asthmatics with 15 in treatment group • 1 and 5 years post bariatric surgery	• Bariatric surgery resulted in improvement in asthma control and QoL at 1 and 5 years.
	Baltieri 2018 [93]	• 19 asthmatics before, 6 and 12 months after bariatric surgery	• Bariatric surgery resulted in significant improvement in systemic (IL-8, CRP, leptin, TNF-α, IL-6, and adiponectin) and pulmonary (sputum TNF- α) inflammatory markers as well as asthma activity scores but nor lung function.
	Guerron 2018 [94]	• Retrospective data analysis on 751 asthmatics undergoing bariatric surgery	• Bariatric surgery significantly decreased asthma medication use starting at 30 days post-operative and up to 3 years.
Obesity and biologic agents in asthma	Ortega 2014 [95]	• Cluster analysis of DREAM study data [96] for mepolizumab	• In patients with high airway reversibility, obese patients had a higher exacerbation reduction with mepolizumab than non-obese patients.
	Sposato 2018 [97•]	• Retrospective data analysis on 340 patients being treated with omalizumab	• Age, obesity, comorbidities, smoking habits, nasal polyps, allergic poly-sensitization might reduce omalizumab effectiveness.

ICS inhaled corticosteroids, *vs* versus, *LABA* long acting beta agonist, *BMI* body mass index, *LTRA* leukotriene receptor antagonist, *Dex* dexamethasone, *MKP-1* mitogen-activated protein kinase phosphatase-1, *ED* emergency department, *GERD* gastroesophageal reflux disease, *AHR* airway hyperresponsiveness, *QoL* quality of life, *RCT* randomized control trials, *IgE* immunoglobulin E, *IL* interleukin, *CRP* C-reactive protein, *TNF* tumor necrosis factor

Conclusion

The rising incidence and cost of asthma with obesity represents an urgent public health need. Our understanding of the pathophysiology of asthma is growing, but many of the current models have difficulty incorporating the effect of obesity. There is promising early epigenetic and genetic data on obese asthmatics that will continue to evolve with the growing field of genomics; however, the most widely studied mechanisms rely on inflammation. The pro-inflammatory effect of obesity is associated with various pathologic cytokines (such as TNF-α, IFN-γ, IL-4, and IL-17A) that have been shown in mouse models to correlate with asthma and may eventually be therapeutic targets along with the microbiome. There unfortunately has been very sparse mechanistic research done on human subjects for the obese asthma population which limits the applicability of this information in clinical practice.

The obese asthma patient tends to be more symptomatic, poorly controlled, and less responsive to ICS than their lean counterparts, and these patients cluster into unique phenotypes in several large asthma studies (typically late onset/female/less atopic vs. early onset/atopic/marked reduction in lung function). These phenotypic distinctions have become increasingly important since essentially all commonly used asthma diagnostic tools (PFTs, methacholine challenge, FeNO, IgE, peripheral eosinophil count) have been shown to be potentially inaccurate in the setting of class II or III obesity. Managing these patients can be particularly challenging since their symptoms can be exaggerated, and there is a tendency not to respond as well to standard therapies. Caring for these patients requires a multimodal clinical approach focusing on inhaler technique, weight loss, and, when appropriate, the use of advanced therapies such as biologics or bronchial thermoplasty even in the absence of traditional supporting criteria. There remains substantial progress to be made in this challenging population.

Compliance with Ethical Standard

Conflict of Interest Njira Lugogo reports grants, personal fees, and non-financial support from GSK; grants and personal fees from AstraZeneca; personal fees from TEVA; grants and personal fees from Genentech; grants and personal fees from SANOFI/Regeneron; and personal fees from Norvartis outside the submitted work. Arjun Mohan, Jon Grace, and Bonnie Wang declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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