Clinical Characteristics and Management Strategies for Adult Obese Asthma Patients

Sherry Farzan1–4, Tyrone Coyle1–3, Gina Coscia1–3, Andre Rebaza2,5, Maria Santiago2,5

1Division of Allergy & Immunology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health System, Great Neck, NY, USA; 2Department of Pediatrics, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health System, Queens, NY, USA; 3Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health System, Manhasset, NY, USA; 4Institute of Health System Science, Feinstein Institutes for Medical Research, Northwell Health System, Manhasset, NY, USA; 5Division of Pediatric Pulmonology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health System, New York, NY, USA

Correspondence: Sherry Farzan, Division of Allergy & Immunology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health System, 865 Northern Blvd, Suite 101, Great Neck, NY, 11021, USA, Tel +1 516-622-5070, Fax +1 516-622-5060, Email sfarzan@northwell.edu

Abstract: The rates of asthma and obesity are increasing concurrently in the United States. Epidemiologic studies demonstrate that the incidence of asthma increases with obesity. Furthermore, obese individuals have asthma that is more severe, harder to control, and resistant to standard medications. In fact, specific asthma-obesity phenotypes have been identified. Various pathophysiologic mechanisms, including mechanical, inflammatory, metabolic and microbiome-associated, are at play in promulgating the obese-asthma phenotypes. While standard asthma medications, such as inhaled corticosteroids and biologics, are currently used to treat obese asthmatics, they may have limited effectiveness. Targeting the underlying aberrant processes, such as addressing steroid resistance, microbiome, metabolic and weight loss approaches, may be helpful.

Keywords: asthma, obesity, body mass index, BMI

Introduction
The CDC reported an asthma prevalence of 8.0% in US adults based on the 2019 National Health Interview Survey (NHIS). Obesity is an important risk factor for asthma incidence and asthma morbidity in children and adults. In 2010, the obesity rate among adults with current asthma (38.8%) was significantly higher than the rate among adults without asthma (26.8%).1,2 Women have a higher asthma prevalence, and some studies indicate that the impact of obesity appears to be more profound in this population. Obese women have 6–7% higher prevalence of asthma than non-obese women. Obesity has been associated with the development of asthma, worsening asthma symptoms, and poor asthma control. Up to 60% of severe asthmatics are obese. This leads to increased medication use and hospitalizations.1–5

A meta-analysis in 2007 of seven prospective studies involving more than 300,000 adults revealed that overweight and obese individuals have 50% increased risk of a new diagnosis of asthma. The odds ratio of incident asthma was 1.5 in overweight individuals with a body mass index (BMI) ≥25 and 1.9 in obese subjects (BMI > 30), compared to normal-weight individuals. Sex did not seem to be a significant modifier of overweight or obesity and asthma risk. The odds ratio of asthma over 1 year follow-up was 1.46 for males and 1.68 for women. The risk increases in non-allergic asthmatics. Effectively, 250,000 new cases of asthma per year in the United States are related to obesity.6,7

The economic cost and overall morbidity of both asthma and obesity underlies the importance of understanding the asthma–obesity interaction. This review of the relationship between asthma and obesity describes clinical insights into the asthma-obesity phenotypes in adults, pathophysiology, effect of medical strategies and the role of surgical and non-surgical weight loss strategies.

Asthma Obesity Phenotypes
Obesity may have a role in the development, severity and control of asthma, but it remains to be established if obesity drives the development of asthma or is a confounder or comorbidity. Current understanding of asthma encompasses...
identification of multiple subgroups or phenotypes, based on clinical characteristics, triggers or general inflammatory processes and response to therapy. Several asthma-obese phenotypes in adults have been identified using unbiased analytical approaches. The origins of the asthma-obesity association and asthma-obesity phenotypes are complex and highly variable between individuals. Asthma associated with obesity may consist of a form of late-onset asthma induced by obesity or a form of early-onset asthma where pre-existing symptoms are aggravated by weight gain. There are differences between obese and non-obese asthmatics, but the studies also demonstrate that asthma phenotypes are heterogeneous among obese individuals, particularly regarding degree of control and response to inhaled corticosteroid (ICS) treatment.

Late-Onset Obese-Asthma Phenotype
Cluster analysis has identified a unique asthma-obesity phenotype predominantly in females with late age of onset and decreased Th2 inflammation that is refractory to conventional asthma treatment, particularly ICS. It is proposed to have little or no eosinophilic inflammation and is driven by changes in airway structure and function. Halder et al performed a cluster analysis in asthmatics followed in primary and secondary care settings. Patients followed in primary care had mild to moderate asthma. More females (81%) were found in the asthma-obesity group with later onset of asthma (mean age of onset 35.3 ± 19 yr.), less atopy and more neutrophilic inflammation compared to other groups. Fractional exhaled nitric oxide (FeNO) and percentage of sputum eosinophils were lower. Another obese cluster was found in the refractory/secondary care group, but with lower age of asthma onset (15.4±15.2 yr), more symptoms and more missed appointments. Analysis of patients in the NIH Severe Asthma Research Program (SARP) by Moore et al also identified an asthma-obesity cluster consisting mainly of older women (mean age, 50 years; range, 34–68 years) with the highest body mass index [BMI] (58% with BMI >30) and late-onset asthma (all older than 23 years of age), who were less likely to be atopic (64% with > one positive skin prick test). Despite a shorter reported duration of asthma, subjects in this cluster had decreased baseline pulmonary function (71% with FEV₁ <80% predicted). These subjects reported complicated medical regimens, with more than half describing treatment with three or more asthma drugs (one of which was frequently high-dose ICS) and 17% received regular systemic corticosteroids. Despite this increased reliance on medications, they reported higher health-care utilization (especially the need for oral corticosteroid bursts) and daily asthma symptoms. Health-care utilization appeared out of proportion to the degree of airflow obstruction. The clinical characteristics of this group highlighted the relationship between obesity, level of asthma symptoms, and health-care utilization.

Early Onset Obese-Asthma Phenotype
Asthma complicated by obesity is usually early in onset with eosinophilic inflammation and high levels of serum IgE. Asthma control in these obese early-onset asthmatics from the SARP cohort was worse than in non-obese asthmatics, with a 3-fold increase in hospitalizations and a 6-fold increase in intensive care admissions compared to non-obese asthmatics. Obese early-onset asthmatics were more likely to have continuous wheeze, nocturnal asthma symptoms, lower asthma-related quality of life, and severe asthma compared to leaner early-onset asthmatics. This phenotype is associated with more severe airway obstruction and airway hyperresponsiveness compared to lean asthmatics with early-onset asthma. Increased eosinophilic inflammation, glucocorticoid insensitivity and physical inactivity may contribute to the development of this phenotype. Sutherland described clusters of obese versus non-obese asthmatic patients enrolled in clinical trials by the NHLBI Asthma Clinical Research Network. BMI was the most significant determinant of cluster membership (F = 57.1, p < 0.0001) followed by asthma symptoms (F = 44.8, p < 0.0001). Patients in the obese asthma clusters were classified as controlled (cluster 3) or uncontrolled (cluster 4). Disease onset in the uncontrolled obese asthmatics was significantly younger, 10.0 years compared to 16.1 years for the controlled obese asthmatics (p < 0.05). Uncontrolled obese asthmatics had persistently high symptom expression and persistently poor control. The uncontrolled obese asthmatics had the highest concentration of FeNO at 24.8 ppb and the greatest degree of airway hyperresponsiveness to methacholine among all the groups. Serum IgE and high sensitivity C-reactive protein (hsCRP) were elevated in obese asthmatics compared to non-obese asthmatics but did not differ significantly between obese asthma clusters. Obese individuals shared similar degrees of lung function impairment,
expression of adipokines, atopy and systemic inflammation (eg, hsCRP) compared to non-obese asthmatics. The patients in the uncontrolled asthma-obesity group had asthma of childhood onset, greater airway hyperresponsiveness to methacholine, greater eosinophilic airway inflammation, persistent symptoms and poor asthma control despite treatment with ICS. Glucocorticoid sensitivity was determined by expression of glucocorticoid receptor alpha (GCRα) and dexamethasone–induced expression of MAP kinase phosphatase-1 (MKP-1), an anti-inflammatory marker of glucocorticoid-induced activation. Obese asthmatics had a 25% lower expression of GCRα compared to non-obese asthmatics. Expression of GCRα in obese asthmatics was significantly and positively correlated with baseline log-transformed expression of MKP-1. A significant positive correlation between GCRα induction and dexamethasone induced MKP-1 expression was found in obese asthmatics. The insensitivity to glucocorticoids in obese asthmatics was directly associated with the degree of systemic inflammation, as indicated by an inverse association with hsCRP and GCRα. Increased production of obesity-related inflammatory cytokines may inhibit induction of MKP-1 by glucocorticoids. Enhanced glucocorticoid insensitivity was also demonstrated in patients with reduced serum 25(OH) vitamin D levels.17

Neutrophilic Obese-Asthma Phenotype

Scott10,15 proposed a neutrophilic obese-asthma phenotype in a study demonstrating increased neutrophilic inflammation with distinct differences in males and females. A greater proportion of obese female asthmatics with late-onset asthma had neutrophilic asthma (airway neutrophils >61%) compared to nonobese asthmatic females (42.9% vs 16.2% p = 0.017). Levels of serum IL-6 were significantly higher in obese asthmatic females. When stratified by sex, a positive association between total plasma saturated fatty acids and sputum neutrophil percentages were found in asthmatic males (B-coefficient (95% CI) 0.108 (0.036–0.180); p = 0.004). Levels of monounsaturated fatty acids in males were associated with reduced neutrophilic inflammation. While obese and non-obese asthmatics had similar lung function, obese subjects were on a higher dose of ICS. Steroid resistance in obese patients may be related to neutrophilic inflammation. Obesity-induced increase in sputum neutrophils has been associated with increases in sputum IL-17. IL-17, which has been associated with poorer asthma control and lung function, may promote obesity–induced increase in sputum neutrophilia. Further studies are needed to better define this phenotype and establish its clinical characteristics.

Pathophysiology

While the different asthma phenotypes likely represent different endotypes, and certain pathophysiologic mechanisms may be more prominent in specific forms of obesity-related asthma, a high degree of overlap can be expected. The clinical presentation of obesity-associated asthma in a specific individual may have its underlying mechanisms based on a combination of mechanical, immunological, metabolic and microbiome processes. To better understand how obese asthmatics arrive at their clinical presentation, and ultimately what is the best approach to treatment, the underlying pathophysiologic mechanisms must be elucidated.

Mechanical Effects

In the late-onset non-atopic obese asthma phenotype, the pathophysiology seems to be mediated at least in part by mechanical changes; however, it may be possible that some of these changes are seen in early-onset obese asthmatics as well. In the obese state, the presence of excess fat both around the trunk and in the thoracic cavity can cause reduction in all lung volumes, but mostly in the functional residual capacity (FRC) and expiratory reserve volume (ERV). In fact, the reduction in FRC results in a decrease in ERV and flow.18 FEV1/FVC ratio is well preserved or increased in obesity, since both are affected to the same extent.19 As a result of these changes, obese patients are breathing at lower lung volumes, which in turn, leads to greater airway hyperresponsiveness and greater collapsibility of small airways.20 The heightened airway hyperresponsiveness is probably due to reduction in the tethering forces of the parenchyma on the attached airway, leading to airway narrowing and early closure of peripheral airways. This increases airway resistance, leads to limitations in expiratory flow when sitting, and even more so when supine.21 In fact, weight loss in late-onset non-atopic asthmatics improves airway hyperresponsiveness.22 Similarly, a small study demonstrated that bariatric surgery resulted in greater improvements in peripheral airway resistance, as captured by impulse oscillometry, but not by spirometry, in severely obese females.23 Furthermore, obesity is associated with greater airway compliance and increased airway wall
Together, the change in airway mechanics leads to greater airway reactivity and air trapping with hyperinflation, and the mechanical changes may promote an inflammatory response in the airway as well. Alveolar ventilation can also be affected by obesity since airway closure prevents gas exchange, causing ventilation-perfusion mismatch. Distribution and degree of adiposity in the trunk, as opposed to other areas, may be a risk factor for why some obese individuals and not others develop late-onset non-atopic asthma with these mechanical changes.

**Inflammatory Changes**

For many phenotypes, asthma is an immunologically mediated disease. Furthermore, adipose tissue is an immunologically active organ, which contributes to the systemic inflammation of obesity. In addition to the adipocytes participating directly as secretors of immune mediators, up to 10% of non-adipose cells are lymphocytes, and even more can be macrophages. The combined immunologic effects of these two conditions contribute to the phenotypic manifestations in obese asthmatics.

**Effects on Th2 Disease**

Early-onset obese asthma is a Th2- high disease, with increased serum IgE levels, peripheral and tissue eosinophils, with associated increases in IL-4, IL-13 and IL-5. However, this pro-inflammatory Th2 state is mitigated by the immune suppression seen in obesity on several levels. CD4 function is decreased in obesity. There is Th1 skewing with the secretion of TNF-α, and Th2 functions are blunted in obesity. In obese individuals, Th1 and TH17 cells are increased relative to Th2 and regulatory T cells in adipose tissue. The downstream effects of this shift to Th1 in obesity are observed with respect to eosinophils. While submucosal airway eosinophils were increased in obese versus lean asthmatics, sputum eosinophils are decreased in these patients. On the other hand, levels of IL-25, which is released by airway epithelial cells and activate innate lymphoid cells (ILC) to produce IL-13 and IL-5, are increased in obesity. Depending on the murine model of obesity and asthma, airway eosinophilia can be inhibited or promoted.

**Role of Adipokines**

The antagonistic adipokines, leptin and adiponectin, which are increased and decreased, respectively, in obesity, may also play a role in the pathophysiology of obesity-associated asthma. Leptin is associated with higher markers of atopy and airway hyperreactivity and increases proinflammatory cytokine TNF-α and IL-6 expression from adipose tissue. Leptin is also associated with proliferation and survival of Th2 cells, ILC type 2 (ILC2) cells, as well as increased expression of type 2 cytokines, IL-4, IL-5 and IL-13. Leptin inhibits the activity and growth of regulatory T cells. In contrast, adiponectin, suppresses TNF-α and IL-6, promotes expression of anti-inflammatory cytokines such as IL-10, and mitigates airway hyperactivity and allergic airway inflammation. There are receptors for both leptin and adiponectin expressed on respiratory epithelial cells, therefore these adipokines likely have far-reaching effects in the lung.

**Role of Macrophages**

Adipose tissue macrophages play several roles in promoting the inflammatory state of obesity. As adipose tissue expands, adipocytes undergo hypoxia, resulting in necrosis that attracts pro-inflammatory macrophages. Along with the dramatic increase in the number of adipose tissue macrophages, a shift from M2 macrophages to M1 macrophages also occurs with resulting elaboration of the pro-inflammatory cytokines, TNF-α, IL-1β and IL-6. Together, the adipocytes and macrophages produce pro-inflammatory adipokines and other cytokines, creating the inflammatory state of obesity. This is reflected by increased C-reactive protein in obese asthmatic adults when compared to their normal weight counterparts. Macrophages also promote Th1 skewing of T cells, which mitigates any baseline Th2 inflammation.

Each of the cytokines perpetuated by adipose tissue macrophages can play a role in the pathophysiology of obesity-associated asthma. For example, in mice fed a high fat diet, IL-1β induces innate lymphoid cell type 3 (ILC3) in the lung to secrete IL-17A, which in turn, triggers airway inflammation and hyperresponsiveness. This pathway is dependent on NLRP3 (NLR family, pyrin domain containing 3) and IL-17A in mice. The elevated levels of ILC3 in the BAL of severe asthmatics suggest a similar pathway may be at play in humans.
asthma. Serum IL-17A is elevated in obesity and sputum IL-17A is increased in obese versus lean asthmatics, suggesting that IL-17A may provide a link between obesity and asthma. Sputum neutrophils are elevated in obese asthmatic women, and an increase in sputum neutrophils is associated with elevated sputum IL-17, and with poor asthma control. Working in concert with IL-1β elaboration from adipose tissue, saturated fatty acids, cholesterol, cholesterol crystals and excess oxidative stress activate the NLRP-3 inflammasome, which acts on enzymes that activate IL-1β from its pro-form, which then promotes inflammation as above. NLRP3 is also critical in triggering inflammation related to diabetes associated with obesity.

IL-6 is a pro-inflammatory cytokine involved in the activation of neutrophils and their production of IL-17 in asthma. Adipose derived dendritic cells secrete IL-6, which then promotes Th17 differentiation and subsequent neutrophilic airway inflammation in asthma. Neutrophils are also the main source of IL-6 in the asthmatic airway. In a study involving two cohorts, non-severe and severe asthmatics, IL-6, which is a marker of obesity-related systemic inflammation and is elevated in metabolic syndrome, was associated with increasing BMI, hypertension, diabetes, severe asthma and poor asthma control as demonstrated by worse lung function and more exacerbations. In mice, IL-6 deficiency improves airway hyper-responsiveness and eosinophilic inflammation. Elevated IL-6 and signaling through the IL-6 trans signaling pathway characterizes a specific subset of asthmatics with frequent exacerbations, eosinophilia and submucosal macrophage and T cell infiltration.

TNF-α levels are elevated in patients with neutrophilic asthma and in patients with severe steroid-resistant asthma. TNF-α promotes broncho-constriction and airway hyperreactivity in murine models. Additionally, in an obese mouse model, TNF-α and macrophages were necessary for airway hyperreactivity. TNF signaling in ILC2s induces airway hyperreactivity in mice through the elaboration of multiple cytokines, IL-5, IL-6 and IL-13, among others. A small study suggested that elevated TNF-α levels could result in reduced surfactant A in obese asthmatics, which then impairs eosinophil resolution, resulting in an eosinophilic phenotype.

In addition to the heightened inflammation orchestrated by macrophages in adipose tissue, there is also macrophage dysfunction that may play a role in asthma. Efferocytosis, an anti-inflammatory process in which M2 macrophages remove apoptotic cells through phagocytosis, is blunted in obese asthmatics in a dose-dependent manner, and inversely associated with BMI and measures of oxidative stress. Conversely, efferocytosis is directly correlated with GR-α expression and MPK-1 induction by dexamethasone in peripheral blood mononuclear cells (PBMCs), markers of steroid responsiveness. Interestingly, efferocytosis is enhanced by glucocorticoids and leads to the production of anti-inflammatory mediators, such as IL-10, TGF-β and prostaglandin E2.

Innate lymphoid cells respond to intrinsic damage signals and also play a role in asthma pathogenesis. While ILC3s seem to perpetuate a non-atopic form of asthma, ILC2s produce IL5 and IL-13, which are critical in atopic asthma, and the levels of these cytokines are heightened in obese mice. The Th2 cytokines produced by ILC2 cells trigger M2 macrophages to produce IL-6, TGF-β and IL-10, which can have far reaching affects and contribute to the low-grade systemic inflammation of obesity.

The multitude of effects of obesity on systemic and airway inflammation, affecting both the Th1 and Th2 axes, create a complicated picture of how the immune system is involved in the pathophysiology of obesity-associated asthma.

Role of Mitochondrial Dysfunction
In addition to serving as the cell’s source of energy, mitochondria also sense dangers and signal threats. This results in release of reactive oxygen species and triggering the cellular danger response system. When this process occurs inappropriately, a proinflammatory cascade resulting in disease could occur. This oxidative stress reflects an imbalance between oxidative and nonoxidative processes.

Mitochondrial function is primarily determined by genetic and epigenetic factors, but other issues such as excess caloric and fat intake can modify function. The latter two can lead to oxidative stress which can cause cellular damage and insulin resistance. Mitochondrial dysfunction results in the increase in certain metabolites such as homocysteine and asymmetric dimethyl arginine (ADMA), which reduce arginine bioavailability, interferes with NO synthesis, and leads to oxonitrative stress in epithelial and vascular endothelial cells. This is the biochemical aberrancy seen with the metabolic syndrome.
Nitric oxide is a gaseous transmitter involved in smooth muscle relaxation, bronchodilation, mucociliary function, restoration of barrier dysfunction after wound repair, host defense and mitigation of airway inflammation, however excess levels are produced in atopic asthmatic airways due to effects of Th2 cytokines on inducible nitric oxide synthase. L-arginine is a substrate for NO synthase (NOS). Abnormalities in L-arginine, and therefore NO metabolism, can lead to NO uncoupling and oxidative stress (due to excess anion superoxide). NOS uncoupling is caused by deficiency of L-arginine, and results in preferential production of anion superoxide instead of NO. Arginase, an enzyme that metabolizes arginine, and results in arginine deficiency, is elevated in asthma and obesity. Asymmetric dimethyl arginine (ADMA), an inhibitor of NOS, is a product of regular protein degradation. ADMA can be further metabolized by dimethylarginine dimethylaminohydrolase (DDHA). As a result, low L-arginine and high ADMA, as reflected by the L-arginine/ADMA ratio in airway epithelial cells, can lead to reactive oxygen and nitrogen species, increasing the overall oxidative stress. The reduced ratio of L-arginine/ADMA reflects the elevated level of oxidative stress and reduced NO bioavailability in the airway that is promoted by both obesity and asthma and prevents normal bronchodilation of the airway.

Mitochondrial dysfunction has also been demonstrated in asthma and is associated with increased ADMA, which along with IL-4 in atopic asthma, induces oxonitrative stress and a cellular hypoxic response, and is associated with severe asthma in mice. ADMA and IL-4 together trigger further mitochondrial dysfunction. This sets up a vicious cycle where obesity and asthma can exacerbate each other.

The airways of obese asthmatics are NO deficient reflecting loss of the physiologic function of NO. The mitochondria in airway epithelial cells of obese asthmatics undergo higher rates of respiration and produce more oxidants than those of their lean counterparts, but due to decreased nitric oxide bioavailability, nitric-oxide-dependent inhibition of mitochondrial respiration is prevented. The resulting production of reactive oxygen species can activate the inflammasome and cause mitochondrial dysfunction. In the airway, this results in higher levels of lipid peroxides, such as 8-isoprostanes and 4-hydroxynonenal, which are elevated in asthma and obesity, and are associated with lower lung function and greater morbidity. Also, 13-S-hydroxyoctadecadienoic acid (13-S-HODE), a lipid metabolite derived from linoleic acid, drives severe asthma in an experimental model. The increase in oxidative stress, reflected by a reduced L-arginine/ADMA ratio is associated with reduced lung function and asthma QoL. The level of oxidative stress is associated with more severe asthma and is not mitigated by ICS. Levels of oxidative stress are associated with increased TGF-β1 expression, which in turn leads to airway remodeling that does not respond to ICS. Obese patients with severe late-onset asthma who had a lower L-arginine/ADMA ratio had more severe asthma symptoms, decreased exhaled nitric oxide and IgE levels. In addition, increased oxidative and nitrosative stress can result in post-translational modification and activation of histone deacetylase 2 (HDAC2) which is critical for the downstream effects of steroids in asthmatics, thus posing as the possible link between obese asthma and poor response to glucocorticoids. Promulgating the oxidative stress described above, there is also a decrease in the antioxidant defenses such as glutathione (major airway antioxidant) and superoxide dismutase. Overweight and obese children are more significantly affected by pollutants and irritants, especially nitrogen oxide, particulate matter and ozone, likely due to the dysfunctional pathways designed to manage oxidative stress.

Microbiome, Diet and Nutrition

Microbiome

The microbiome is the collective genome of the trillions of bacteria which live in the human intestinal tract. Early life establishment of the microbiome due to certain exposures such as early antibiotic use, Caesarean section, formula feeding and lack of exposure to animals, increase the risk of atopic asthma and obesity due to microbial dysbiosis. It is possible that the skewed microbiome leads to obesity, which in turn increases the risk of asthma through the mechanisms below.

The gut microbiome is less diverse in obese individuals compared to lean individuals. The more diverse the microbiome, the greater the mucosal immune defense. Obesity results in microbiome dysbiosis, reduced microbial diversity and an elevated ratio of Firmicutes to Bacteroides, which decreases with weight loss. The resulting decrease in mucosal immune defense, which is usually provided by a diverse microbiome, and the resultant increase in intestinal permeability may contribute to the increased level of serum LPS found in the plasma of obese individuals, the resulting
endotoxemia causing activation of nuclear factor kappa B (NF-κB) pathways, and increased expression of IL-6 and TNF-α. Treatment with antibiotics in mice mitigates the LPS endotoxemia and its associated inflammation, oxidative stress and body weight gain.

Some gut bacteria can convert polysaccharides into short chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, which human intestinal enzymes cannot do. These SCFAs can be converted into ATP by the host. In mice, a high fiber/low fat diet increases the circulating levels of SCFA. SCFAs lead to enhanced hematopoiesis of dendritic cell (DC) precursors from bone marrow, but these DC have impaired ability to activate Th2 effector cells in the lung. With a high fiber diet, there was increased *Bacteroides*, leading to the increased synthesis of the short chain fatty acids, acetate, butyrate and propionate and reduced allergic inflammation in the lung. Propionate, in turn, is associated with reduced Th2 effector functions. Receptors for SCFAs can be found in non-gastrointestinal organs, suggesting that the effects of the microbiome can be as far-reaching as the lungs. SCFAs also lead to the increased development of anti-inflammatory colonic T cells. In addition, SCFAs (propionate and butyrate) decrease LPS-induced NFκB activation and pro-inflammatory ROS and TNF-α production by neutrophils, likely by HDAC inhibition. In contrast, a low fiber/high fat diet induces dysbiosis, inhibits Treg function, and increases Th2 airway inflammation. In mice, a diet low in fiber was associated with increased airway eosinophils, Th2 cytokines, and IL-17A, and also promoted a gut microbiome with increased ratio of *Firmicutes* to *Bacteroides*. In contrast to SCFAs, levels of bile acids are increased in the setting of obesity-induced gut dysbiosis, and the levels of specific bile acids correlate with lung function decline.

The gut microbiome may affect obesity and asthma through mucosal communication between the intestinal and respiratory tracts when antigens are presented in the gut, and there are immunostimulatory or immunomodulatory effects in the lung. Composition of the gut microbiota may affect systemic levels of IL-17A, which are critical for neutrophilic recruitment. As noted above, Serum IL-17A is elevated in obesity and sputum IL-17A is increased in obese versus lean asthmatics, suggesting that IL-17A may provide a link between the microbiome, obesity and asthma.

The microbiome is not limited to the gut. The microbiome of the lung, mouth, nose and gut are different in asthmatics and obese individuals when compared to controls, but have similarities to each other, which demonstrates an additive effect in obese asthmatics, although the subjects in this study were mainly atopic. In severe asthmatics, the lung microbiome differs in obese and non-obese.

**Diet and Nutrition**

While the microbiome can clearly affect airway inflammation in obese asthmatics, components of the diet may provide a mechanism as well. Ingestion of a high fat meal acutely increases sputum neutrophilia, Toll like receptor 4 expression, and reduces bronchodilator response. A high fat diet is also associated with airway hyperresponsiveness in humans, although data are limited. A Western diet (high in palmitic acid) was associated with a greater inflammatory response than a Mediterranean diet (high oleic acid), as demonstrated with increased levels of TNF-α, IL-10, IL-18 and IL-1β. In animal models, a high fructose diet, even without obesity, is associated with elevated ADMA, reduced nitric oxide, and increased airway resistance. As discussed above, the abnormalities in NO metabolism are likely to play a role, through diet as well as obesity. Also, as noted above, in mice fed a high fat diet, airway hyperresponsiveness was associated with activity of ILC3, which produced IL-17A, as well as by IL-1β and NLRP3 inflammasome.

Fatty acids, which are elevated after a high fat meal, and in obese individuals, can activate TLR4, which then in turn, activates the NLRP3 inflammasome, which activates caspase-1 to cleave IL-1β making it functional. The relevance of this pathway is demonstrated by increased levels of IL-1β, TLR4 and NLRP3 in the lungs of obese asthmatics. In contrast, fruits and vegetables, which are high in antioxidants that can play a role in relieving the antioxidant stress of both asthma and obesity, have been demonstrated to improve asthma control.

Vitamin D deficiency is associated with excess weight as well as with asthma exacerbations, suggesting that it may play a role in the association between asthma and obesity. While many studies evaluating the role of vitamin D supplementation have not been performed, one short-term study did not show an improvement in control in asthmatics, but obese asthmatics were not specifically studied.
Comorbidities
Comorbidities such as metabolic syndrome, diabetes, hypertension, obstructive sleep apnea, depression and gastroesophageal reflux can not only lead to symptom misattribution, but also may play a role in exacerbating co-existent asthma in the obese. In post-menopausal women, the incidence of metabolic syndrome was similar among asthmatics and non-asthmatics, but the former had greater insulin resistance. Although the findings were not large in magnitude, patients with metabolic syndrome were found to have a greater degree of airway obstruction in several studies, and this was associated with their level of peripheral eosinophilia. In fact, patients with metabolic syndrome who underwent bariatric surgery did not have as much improvement in their asthma control as those who did not have metabolic syndrome, suggesting that the systemic inflammation due to underlying metabolic dysregulation, and not the excess weight, may be the culprit. High insulin levels, often associated with obesity, can trigger both centrally and peripherally mediated vagal-induced bronchoconstriction.

Genetics
Twin studies, family-based linkage studies and genome-wide association studies support the idea that obesity and asthma share a genetic basis. Furthermore, a common genomic inversion protects against both asthma and obesity.

Management
Inhaled Corticosteroids
The effectiveness of ICS has been well established in the management of asthma. The presence of obesity is also associated with a higher inflammatory state. When assessing pulmonary function, particularly FEV1, the treatment time from onset to peak FEV1 was longer in obese patients treated with ICS + LABA compared to patients with a normal BMI. A recent meta-analysis highlighted obese patients also had significantly lower FEV1 compared to normal BMI patients, and more likely to be on controller medications such as ICS, ICS + LABA, and oral corticosteroids. Studies have also noted a higher prevalence of higher ICS dose in obese patients compared to non-obese, reflective of asthma severity in this cohort. In addition, obesity not only was associated with a reduced response to ICS + LABA with regard to both FEV1 and FEV1/FVC ratio, but also was associated with a reduced response of ICS on FeNO.

When assessing asthma control, a similar relationship was described in a study that found asthma control days (ACD) also decreased significantly with increasing BMI in patients treated with beclomethasone. Obese patients also were less likely to achieve asthma control with ICS and ICS + LABA compared to non-obese patients and were 2.7 times less likely of achieving control compared to normal BMI patients. This further questions the effectiveness of ICS as a controller medication the higher the patient’s BMI.

The negative correlation between BMI and steroid effectiveness has been further studied in vitro, noting a blunted glucocorticoid induction of biomarker mitogen-activated protein kinase phosphatase-1 (MKP-1) in peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage (BAL) in obese asthmatics compared to non-obese patients. The reduction in (MKP-1) was also observed per unit increase in continuous BMI. In addition, baseline tumor necrosis factor (TNF)-α expression was enhanced in both PBMCs and BAL in obese asthmatics, highlighting glucocorticoid insensitivity in this population. Obese patients not only have a higher inflammatory response compared to non-obese patients but are at risk for decreased forced vital capacity (FVC) and thus impairment in lung function secondary to a mechanical restrictive defect from distribution of body fat. In this scenario, ICS may not be as effective in obese patients who have decreased lung compliance secondary to body habitus.
Characterizing the inflammatory phenotype in obese patients can also be predictive of ICS response, where obese patients with eosinophilic inflammation are likelier to demonstrate effective response to ICS, whereas obese patients with neutrophilic inflammation and decreased FVC are unlikely and may worsen with increase in ICS.\textsuperscript{132,135} Similar association with ICS response and eosinophilic inflammation was also demonstrated in non-obese patients.\textsuperscript{144}

**Montelukast**

The role of leukotriene antagonists, particularly montelukast, in adult obese patients with asthma is limited. Obesity in general has been associated with an increased expression of 5-lipoxygenase pathway and also higher leukotriene production, which raised prospect of montelukast response in obese patients with asthma.\textsuperscript{145} In obese patients with an early onset atopic asthma, montelukast was an effective controller medication in improving asthma control test (ACT) score.\textsuperscript{146} Similarly, asthma control day (ACD) percentage also increased with increasing BMI in patients treated with montelukast.\textsuperscript{140} On the contrary, studies have noted ICS + LABA as well as ICS led to significantly higher forced expiratory volume in one second (FEV1), asthma symptom score, and less albuterol use, compared to montelukast alone, including when considering patient BMI.\textsuperscript{134,147}

**Biologics**

Since obesity-associated asthma includes at least two different phenotypes, the role of biologics may differ within the broad group of patients with the two conditions.

For patients with type 2 inflammation, a broad array of biologics has emerged over the past 20 years, particularly within the last 5 years. These include omalizumab, mepolizumab, reslizumab, dupilumab and benralizumab, in order of FDA approval for asthma. Omalizumab blocks type 2 inflammation through anti-IgE blockade. Mepolizumab and reslizumab block IL-5 directly, and benralizumab blocks the anti-IL-5 receptor, all leading to reduction of eosinophil counts. Dupilumab works uniquely by blocking both IL-4 and IL-13 through its antagonism of the IL4Rα. All of the aforementioned biologics block type 2 inflammation, and choice of the ideal agent depends on some key differentiating features such as perennial allergic sensitization, peripheral blood eosinophil count, FeNO, and comorbidities such as atopic dermatitis.

Given the heterogeneity of the mechanisms at play in the obesity-associated asthma phenotype, it is not surprising that biologics may not be equally effective in all patients with obesity. For those obese patients with neutrophilic asthma, or with alterations in the IL-17, IL-22 or IL-6 pathways the existing biologics are not applicable.\textsuperscript{6} Emerging biologics, such as the recently approved tezepelumab, which targets the upstream TSLP pathway, may have a role for obese asthmatics with non-type 2 inflammation. Tezepelumab improves the rate of exacerbations, irrespective of eosinophil count, which may suggest that it may be a promising tool in treatment of obese asthmatics with non-eosinophilic asthma.\textsuperscript{148} For those with type 2 inflammation, the biologics affecting the allergic pathways may be helpful, but not all biologics are equally effective.

As many of these biologics are relatively new, there are limited data on specific efficacy in obese patients, although there are some trends that have emerged over time. Biologics that require weight-based dosing, such as omalizumab and reslizumab, may have less benefit in obese asthmatics. In fact, a recent retrospective review of 340 patients with severe asthma on omalizumab, noted that obese patients, compared to those with normal weight, demonstrated worse outcomes. Specifically, obesity was significantly associated with a greater number of exacerbations, reduced ACT and worse asthma control as defined by the GINA guidelines, controlling for other confounders. Obese asthmatics on omalizumab were also less likely to have an improvement in FEV\textsubscript{1} after omalizumab compared to normal weight subjects.\textsuperscript{149} These findings are not surprising for a weight-based biologic; however, the lack of efficacy may extend beyond dosing issues. A major limitation of this study is the lack of data on possible neutrophilic airway disease in these subjects. Rather than a poor response to Xolair due to obesity, or due to inadequate dosing, it is possible that the subjects were not ideal candidates for Xolair, mechanistically.

In contrast, data for efficacy of dupilumab in obese asthmatics are more favorable. A post hoc analysis of the Phase 3 QUEST study of dupilumab demonstrated that in 1584 patients with elevated peripheral eosinophil counts and FeNO, there was a reduced annualized rate of asthma exacerbations, regardless of demographics. Demographics analyzed were gender, geographic region, age, and BMI. The greatest treatment effects were observed in those with higher blood eosinophil levels and FeNO.\textsuperscript{150}
Similarly, mepolizumab has favorable data for obese asthmatics. A 2021 post hoc meta-analysis of all of four phase IIb/III studies of mepolizumab, in which 32% of subjects reported obesity, there was a reduction in the rate of clinically significant exacerbations, health-related quality of life, and asthma control independent of comorbidities. 151

Given the relatively recent use of biologics in the treatment of asthma, and the emerging understanding of obese asthma phenotypes, elucidation of the interaction between obesity and biologics is an important area for future research.

Microbiome and Metabolic Approaches
Addressing the microbiome and metabolic processes may be critical pathways to consider in the management and treatment of asthma associated with obesity. The microbiome comprises a great diversity of commensal bacteria species that colonize human body tissues and fluids, and dysbiosis is present in asthma and obesity. Aberrant metabolic processes are also present in the obese asthma phenotypes. Addressing the microbiome and metabolic dysfunction in a way that mitigates inflammation and obesity could help in the treatment of obese asthmatics.

Methods to ameliorate gut microbiome dysbiosis have been proposed for obesity management and could have potential in the treatment of obese asthmatics. The use of probiotics is a common technique to modulate intestinal microbiota in the obese. 96 Murine studies have shown probiotic use promotes weight loss115 and reduces inflammatory mediators152 which diminish obesity derived systemic inflammation. A high fiber diet, which increases SCFA concentrations, is another approach to alter the gut microbiota which could prove effective. A murine study showed high fiber diets correlated with reduced allergic airway responses, decreases in serum IgE and IL4 levels, and that this was mediated by SCFAs. In contrast, low fiber diets increased allergic airway disease. 103 A recent NHANES survey demonstrated that a high fiber diet was associated with an increased odds of having asthma, supporting the role of the microbiome in human asthma. 153

Several small human studies support the role of probiotics, which can alter the microbiome favorably, in asthmatic children. Use of probiotics improved lung function, rates of exacerbation and asthma control in children with asthma. 154–156 However, studies in adults are lacking, and probiotics specifically in the obese-asthma phenotype has not been explored. The use of SCFA in the modulation of the unfavorable effects of obese-asthma dysbiosis is yet another potential avenue of investigation.

Bile acids, levels of which are also increased in obese asthmatics, and associated with poor lung function are another potential target. Murine studies with nitro-oleic acid (NO2-OA) demonstrate that treatment with this small molecule electrophile suppresses bile acid production, and is associated with improved lung function. 107 A clinical trial investigating the use of NO2-OA in the treatment of obese asthmatics is underway.

The uncoupling of NO synthase mediated by asymmetric dimethyl arginine has been implicated in the deficiency of nitric oxide in obese asthmatics. The resulting oxidative stress is associated with poor asthma QoL and lung function. 88 L-arginine is the substrate for NO synthase, and L-citrulline, a precursor of L-arginine, has been hypothesized as a potential treatment of obese asthmatics. In a small, proof-of-concept, open-label study, treatment with L-citrulline, improved asthma control and increased FeNO in obese asthmatics. Greater improvements in FEV1 were observed in patients with late-onset asthma. 157 A larger, randomized clinical trial is necessary to confirm these findings. Other components of this pathway, such as arginase, which is upregulated in asthma, could be potential targets for treatment.

Weight Loss Approaches
Given the mechanical, inflammatory and metabolic consequences of obesity that play a role in modifying asthma, addressing obesity through weight loss, has the potential to be an effective approach. Obesity has numerous definitions, but the most prevalent definition is a body mass index (BMI) ≥30 kg/m². BMI classification further categorizes obesity into classes: Class I – 30.0 to 34.9 kg/m²; Class II – 35.0 to 39.9 kg/m²; Class III – ≥40 kg/m². A useful method of evaluating borderline obesity is by measuring abdominal obesity, which is defined as waist circumference ≥40 inches for males and ≥35 inches for females. As a result of the poor asthma control inherent to the obese asthmatic phenotype, exercise intolerance leads to a higher proportion of individuals who are inclined to sedentary lifestyles, and in turn insufficient physical activity tends to worsen obesity, and thus further exacerbating the negative effects. This, in turn, can be compounded by the recurrent or chronic use of systemic steroids, which can lead to further weight gain. Due to the
numerous detrimental effects of comorbid asthma and obesity, weight loss is an attractive approach for optimizing asthma management in obese patients. Numerous studies have demonstrated significant improvements in both asthma symptomatic control and spirometric lung function with sufficient weight loss. Strategies for weight loss can be categorized into non-surgical and surgical weight loss approaches.

Diet and Exercise Induced Weight Loss

Non-surgical weight loss, often referred to broadly as “lifestyle changes,” is frequently utilized as the initial approach for managing obesity. Lifestyle changes include numerous discrete weight loss interventions such as dieting, behavioral counseling and exercise regimens. A review of recent studies that focused on non-surgical weight loss in obese asthmatics revealed a wide range of weight loss strategies and program durations that were employed. Each specific weight loss intervention encompasses a variety of disparate methodologies; dieting can vary from strict calorie-restriction or meal replacement to more patient-centered approaches focusing on nutritional education. It has been hypothesized that simply transitioning from a typical western diet to a Mediterranean diet rich in anti-inflammatory nutrients could both be a viable method of diet while providing an additional benefit of reduced systemic inflammation.

A study of 22 massively obese asthmatics who were assigned to either a diet group or control group resulted in an approximately 15% decrease in body weight on average over 3 months in the diet group. The diet group had significant improvements in asthma control, lung function and asthma quality of life compared to the control group. Özbeş et al investigated a cohort of 55 obese adult asthmatics (median BMI 36.4) which were randomly assigned into a diet group or control group. The mean body weight in the diet group decreased significantly (~4.5 kg) and this correlated with significant improvements in asthma control, quality of life and pulmonary function in the diet group compared to the control group. Of note, patients with 5.0% or greater weight loss had an even more pronounced improvement in FEV1 and FVC values, as well as ACT (Asthma Control Test) and AQLQ (Asthma Quality of Life Questionnaire) scores.

Studies have also indicated a combination of both diet and exercise shows a greater benefit, and so weight loss programs often utilize both approaches simultaneously. Freitas et al investigated a cohort of 55 grade II obese adults with asthma and found a significant difference between a weight loss program with both diet and exercise (consisting of aerobic and resistance muscle training) compared with a diet program with no exercise component. After 3 months, the diet and exercise group showed more significant clinical improvements as compared to the diet-only group, including: number of asthma symptom free days, lower prevalence of developing obstructive sleep apnea and less depressive symptoms.

Surgical Weight Loss

In certain instances, more invasive surgical weight loss techniques may be the preferred option. Surgical weight loss procedures, also called bariatric surgery, are cited as the most effective intervention for producing sustained and significant weight loss. Bariatric surgeries include a variety of surgical techniques including Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion with duodenal switch (BPD/DS), single-anastomosis duodeno-ileo bypass with sleeve gastrectomy (SADI-S) and intragastric balloon. Differing from non-surgical weight loss techniques, bariatric procedures require candidates to meet strict prerequisite criteria. To qualify for bariatric surgery, patients must meet criteria defined as an adult with BMI ≥40 kg/m² without comorbid illness or an adult with BMI 35.0 kg/m² to 39.9 kg/m² and at least one of the following: a serious comorbidity, impaired quality of life or disqualification from other surgeries due to obesity.

Studies on asthmatics after bariatric surgery have reported significant improvements in asthma control, airway reactivity, lung function and reduced asthma exacerbations. A meta-analysis of obese asthmatic adults that underwent bariatric surgery showed a significant increase in FEV1 and FVC after bariatric surgery. A recent retrospective review of 39 studies inclusive of 5185 patients compared non-surgical and surgical weight loss effects on asthma control. Overall, all methods of weight loss led to a reduction or cessation of asthma medication use, significant improvement in symptom scores, improvement in FEV1 and FVC; select studies showed a decrease in inflammatory mediators, improvement in airway hyperresponsiveness and decreased acute asthma-related health-care visits. However, the bariatric surgery cohort showed greater weight loss (22–36%) compared with the non-surgical cohort (4.1–14.2%), and
the bariatric surgery group also showed more consistent improvement with medication use, symptom scores, airway hyperresponsiveness, exacerbations and acute asthma-related health-care visits.\textsuperscript{164}

Available data indicate that all effective weight loss methods are likely to provide benefits in both objective and subjective metrics for obese asthmatic patients. However, weight loss of greater than 5\% of total body weight is likely to produce a more significant improvement. Additionally, data suggest non-surgical approaches that combine diet and exercise offer a more significant clinical improvement than diet alone. Furthermore, surgical weight loss, although invasive and limited by compulsory selection criteria, may offer the greatest overall benefit for both overall weight loss potential and clinical asthma improvement. However, it should be noted that there are significant challenges to achieving effective and sustained weight loss. Less than 2\% of eligible asthmatics undergo bariatric surgery,\textsuperscript{165} which suggests significant apprehension with elective invasive procedures. Non-surgical weight loss methods like low calorie diets can be difficult to maintain long term. Further investigations are needed to improve our understanding of the physiologic and pathologic effects of obesity on asthma, and to determine the most effective strategies for weight loss for individual patients.

### Conclusion

With the rising rates of asthma and obesity in the United States, and the more severe phenotype of these patients, this population has the potential to pose a significant burden on the health-care system. Clarification of the different phenotypes and the underlying pathophysiologic mechanisms is critical for understanding the most effective approaches to treatment for this group of patients. The interplay of mechanical, inflammatory, microbiome and metabolic pathways creates a complicated picture of the obese asthma phenotypes. However, the pathways also provide potential targets for treatment. Although there are multiple categories of medication approved for the treatment of asthmatics, none of them is directed specifically towards obese asthmatics. While weight loss would be ideal in treating not only asthma among these patients, but also the multitude of other obesity-related comorbidities, future research is necessary to hone in on the pathophysiologic pathways contributing to the obese-asthma phenotypes, and the best approaches to treatment.

### Disclosure

The authors report no conflicts of interest in this work.

### References

1. Asthma data, statistics and surveillance; 2021. Available from: http://www.cdc.gov/asthma/most_recent_data/htm. Accessed January 9, 2022.
2. AsthmaStats- asthma and obesity. Available from: https://www.cdc.gov/asthma/asthma_stats/percentage_people_asthma_obese.pdf. Accessed January 17, 2022.
3. Mohan A, Grace J, Wang BR, Lugogo N. The effects of obesity in asthma. \textit{Curr Allergy Asthma Rep.} 2019;19(49). doi:10.1007/s11882-019-0877-z
4. Miethe S, Katsonova K, Karaulov A, Renz H. Obesity and asthma. \textit{J Allergy Clin Immunol.} 2020;146:685–693. doi:10.1016/j.jaci.2020.08.011
5. Peters U, Dixon AE, Forno E. Obesity and asthma. \textit{J Allergy Clin Immunol.} 2018;141:1169–1179. doi:10.1016/j.jaci.2018.02.004
6. Garcia-Rio F, Alvarez-Puebla MJ, Esteba-Gorgojo I. Barranco P and olaguibel jm. obesity and asthma: key clinical questions. \textit{J Allergy Clin Immunol.} 2019;29(4):262–271.
7. Beuther DA, Sutherland ER. Overweight, obesity and incident asthma: a meta-analysis of prospective epidemiologic studies. \textit{Am J Respir Crit Care Med.} 2007;175:661–666. doi:10.1164/rccm.200611-1717OC
8. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular to clinical approaches. \textit{Nat Med.} 2012;18:716–725. doi:10.1038/nm.2678
9. Dixon AE, Poynter ME. Mechanisms of asthma in obesity. Pleiotropic aspects of obesity produce distinct asthma phenotypes. \textit{Am J Respir Cell Mol Biol.} 2016;54:601–608. doi:10.1165/rcmb.2016-0017PS
10. Scott HA, Wood LG, Gibson PG. Role of obesity in asthma: mechanisms and management strategies. \textit{Curr Allergy Asthma Rep.} 2017;17(53). doi:10.1007/s11882-017-0719-9
11. Khalid F, Holguin F. A review of obesity and asthma across the life span. \textit{J Asthma.} 2018;55(12):1286–1300. doi:10.1080/02770903.2018.1424187
12. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. \textit{Am J Respir Crit Care Med.} 2008;178(3):218–224. doi:10.1164/rccm.200711-1754OC
13. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. \textit{Am J Respir Crit Care Med.} 2010;181(4):315–323. doi:10.1164/rccm.200906-0896OC
14. Holguin F, Bleeker ER, Busse WW, et al. Obesity and asthma, an association modified by age of asthma onset. J Allergy Clin Immunol. 2011;128(6):1486–1493. doi:10.1016/j.jaci.2011.03.036
15. Scott HA, Gibson PG, Garg ML, Wood LG. Airway inflammation is augmented by obesity and fatty acids in asthma. Eur Respir J. 2011;38(3):594–602. doi:10.1183/09031936.00139810
16. Sutherland TJ, Cowan JO, Young S, et al. The association between obesity and asthma: interactions between systemic and airway inflammation. Am J Respir Crit Care Med. 2008;178(5):468–475. doi:10.1164/rccm.200802-301OC
17. Sutherland ER, Goleva E, King TS, et al. Cluster analysis of obesity and asthma phenotypes. PLoS One. 2012;7(5):e36631. doi:10.1371/journal.pone.0036631
18. Jones RL, Nzekwu M-MU. The effects of body mass index on lung volumes. Chest. 2006;130:827–833. doi:10.1378/chest.130.3.827
19. Biringer MS, Lewis MI, Liu JT, Mohsenifar Z. Pulmonary physiological changes of morbid obesity. Am J Med Sci. 1999;318:293–297. doi:10.1016/S0002-9629(05)40614-X
20. Ding DJ, Martin JG, Macklem PT. Potential role of the airway wall in the asthma of obesity. J Appl Physiol. 1987;62:1324–1330. doi:10.1152/jappl.1987.62.3.1324
21. Sin DD, Sutherland ER. Obesity and the lung: 4. Obesity and asthma. Thorax. 2008;63:1018–1023. doi:10.1136/thx.2007.086819
22. Sideleva O, Suratt BT, Black KE, et al. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. Am J Respir Crit Care Med. 2012;186:598–605. doi:10.1164/rccm.201203-0573OC
23. Peters U, Hernandez P, Dechman G, Ellsmere J, Maksym G. Early detection of changes in lung mechanics with oscillometry following bariatric surgery in severe obesity. Appl Physiol Nutr Metab. 2016;41(5):538–547. PMID: 27109263. doi:10.1139/apnm-2015-0473
24. Bates JH, Dixon AE. Potential role of the airway wall in the asthma of obesity. J Appl Physiol. 2015;118:36–41. doi:10.1152/japplphysiol.00684.2014
25. Yalcin HC, Perry SF, Ghadiali SN. Influence of airway cell confluence on epithelial cell injury in an in vitro model of airway reopening. J Appl Physiol. 2007;103:1796–1807. doi:10.1152/japplphysiol.00164.2007
26. Brazzale DJ, Preto JF, Schachter LM. Optimizing spirometry function assessments to elucidate the impact of obesity on respiratory health. Respir Med. 2015;20:715–721. doi:10.1111/resp.12563
27. Acosta JR, Douagi I, Andersson DP, et al. Increased fat cell size: a major phenotype of non-obese adipose tissue in non-obese individuals with type 2 diabetes. Diabetologia. 2015;59:560–570. doi:10.1007/s00125-015-3810-6
28. Dixon AE, Pratley RE, Forgione PM, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. J Allergy Clin Immunol. 2011;128:508–515.e1. doi:10.1016/j.jaci.2011.06.009
29. McLaughlin T, Liu LF, Lamendola C, et al. T-cell profile in adipose tissue is associated with insulin resistance and systemic inflammation in humans. Arterioscler Thromb Vasc Biol. 2014;34:2632–2636. doi:10.1161/ATVBAHA.114.304636
30. Desai D, Newby C, Symon FA, et al. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. Am J Respir Crit Care Med. 2013;188:657–663. doi:10.1164/rccm.201208-1470OC
31. van der Wiel E, Ten Hacken NH, van den Berge M, Timens W, Reddel HK, Postma DS. Eosinophilic airway inflammation in subjects with mild-to-moderate asthma with and without obesity: disparity between sputum and biopsies. Am J Respir Crit Care Med. 2014;189:1281–1284. doi:10.1164/rccm.201310-1841LE
32. van Veen HN, Ten Brinke A, Sterk PJ, Rabe KF, Bel EH. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. Allergy. 2008;63:570–574. doi:10.1111/j.1398-9995.2007.01597.x
33. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? Chest. 2008;134:317–323. doi:10.1378/chest.07-2959
34. Marijssse GS, Seys SF, Schelpe AS, et al. Obese individuals with asthma preferentially have a high IL-5/IL-17A/IL-25 sputum inflammatory pattern. Am J Respir Crit Care Med. 2014;189:1284–1285. doi:10.1164/rccm.201311-2011LE
35. Ge XN, Greenberg Y, Hosseinikhani MR, et al. High-fat diet promotes lung fibrosis and attenuates airway eosinophilia after exposure to cockroach allergen in mice. Exp Lung Res. 2013;39:365–378. doi:10.1080/01902148.2013.829537
36. Calixto MC, Lintomen L, Schenka A, Saad MJ, Zanesco A, Antunes E. Obesity enhances eosinophilic inflammation in a murine model of allergic asthma. Br J Pharmacol. 2010;159:657–625. doi:10.1111/j.1476-5381.2009.00560.x
37. Lintomen L, Calixto MC, Schenka A, Antunes E. Allergen-induced bone marrow eosinophilia and airways eosinophilic inflammation in leptin-deficient ob/ob mice. Obesity. 2012;20:1995–1996. doi:10.1038/oby.2012.93
38. Shore SA, Schwartzman IN, Mellema MS, Flynt L, Innrich A, Johnston RA. Effect of leptin on allergic airway responses in mice. J Allergy Clin Immunol. 2005;115:103–109. doi:10.1016/j.jaci.2004.10.007
39. Jeong KY, Lee J, Li C. Juvenile obesity aggravates disease severity in a rat model of atopic dermatitis. Allergy Asthma Immunol Res. 2015;7:69–75. doi:10.4168/aaar.2015.7.1.69
40. Zheng H, Zhang X, Castillo EF, Luo Y, Liu M, Yang XO. Leptin enhances TH2 and ILC2 responses in allergic airway disease. J Biol Chem. 2016;291(42):22043–22052. PMID: 27566543. PMCID: PMC5063987. doi:10.1074/jbc.M116.714317
41. Hasenkrug KJ. The leptin connection: regulatory T cells and autoimmunity. Immunity. 2007;26(2):143–145. doi:10.1016/j.immuni.2007.02.002
42. Masaki T, Chiba S, Tatsukawa H, et al. Adiponectin protects LPS-induced liver injury through modulation of TNF-alpha in KK-Ay obese mice. Hepatology. 2004;40:177–184. doi:10.1002/hep.20282
43. Kumada M, Kihara S, Ouchi N, et al. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation. 2004;109:2046–2049. doi:10.1161/01.CIR.0000127953.98131.ED
44. Periyalil HA, Wood LG, Scott HA, Jensen ME, Gibson PG. Macrophage activation, age and sex effects of immunometabolism in obese asthma. Eur Respir J. 2014;45:388–395. doi:10.1183/09031936.0008514
45. Sharma N, Akkoyunlu M, Rabin RL. Macrophages-common culprit in obesity and asthma. Allergy. 2018;73(6):1196–1205. PMID: 29178573. doi:10.1111/all.13369
56. Chen Y, Tian J, Tian X, et al. Adipose tissue dendritic cells enhances inflammation by prompting the generation of Th17 cells.

55. Halwani R, Sultana A, Vazquez-Tello A, Jamhawi A, Al-Masri AA, Al-Muhsen S. Th-17 regulatory cytokines IL-21, IL-23, and IL-6 enhance neutrophil production of IL-17 cytokines during asthma. *Am J Respir Cell Mol Biol* 2013;49(1):51–59. PMID: 23556258; PMCID: PMC3878353. doi:10.1165/rcmb.2012-02855x.

54. Umetsu DT. Mechanisms by which obesity impacts upon asthma. *Thorax* 2017;72(2):174–177. PMID: 27672120. doi:10.1136/thoraxjnl-2016-209130.

53. Chen J-H, Qin L, Shi -Y-Y, et al. IL- 17 protein levels in both induced sputum and plasma are increased in stable but not acute asthma individuals with obesity. *Respir Med* 2016;112:21–48. doi:10.1016/j.resmed.2016.10.018.

52. Telenga ED, Tideman SW, Kerstjens HAM, et al. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. *Allergy* 2012;67(8):1060–1068. doi:10.1111/j.1398-9995.2012.02855.x.

51. Sumarac-Dumanovic M, Stevanovic D, Ljubic A, et al. Increased activity of interleukin-23/interleukin-17 proinflammatory axis in obese individuals with obesity. *Respir Med* 2016;112:21–48. doi:10.1016/j.resmed.2016.10.018.

50. Umetsu DT. Mechanisms by which obesity impacts upon asthma. *Thorax* 2017;72(2):174–177. PMID: 27672120. doi:10.1136/thoraxjnl-2016-209130.

49. Fernandez-Boyanapalli R, Goleva E, Kolakowski C, et al. Obesity impairs apoptotic cell clearance in asthma. *J Allergy Clin Immunol* 2013;131:1041–1047. doi:10.1016/j.jaci.2012.09.028.

48. Lee HY, Lee HJ, Chang YJ, et al. Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. *Nat Med* 2014;20:54–61. doi:10.1038/nm.3423.

47. Sumarac-Dumanovic M, Stevanovic D, Ljubic A, et al. Increased activity of interleukin-23/interleukin-17 proinflammatory axis in obese women. *Int J Obesity* 2009;33:151–156. doi:10.1038/ijo.2008.216.

46. Telenga ED, Tideman SW, Kerstjens HAM, et al. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. *Allergy* 2012;67(8):1060–1068. doi:10.1111/j.1398-9995.2012.02855.x.

45. Chen J-H, Qin L, Shi -Y-Y, et al. IL- 17 protein levels in both induced sputum and plasma are increased in stable but not acute asthma individuals with obesity. *Respir Med* 2016;112:21–48. doi:10.1016/j.resmed.2016.10.018.

44. Mathews JA, Krishnamoorthy N, Kasahara DI, et al. IL-33 drives augmented responses to ozone in obese mice.

43. Grace J, Mohan A, Lugogo NL. Obesity and adult asthma: diagnostic and management challenges. *Curr Opin Pulm Med* 2019;25(1):44–50. PMID: 30394901. doi:10.1097/MCP.0000000000000531.

42. Mathews JA, Krishnamoorthy N, Kasahara DI, et al. IL-33 drives augmented responses to ozone in obese mice. *Environ Health Perspect* 2017;125(2):246–253. doi:10.1289/EHP272.

41. Bhatraju NK, Agrawal A. Mitochondrial dysfunction linking obesity and asthma. *Ann Am Thorac Soc* 2017;14(Supplement_5):S368–S373. PMID: 29161084. doi:10.1513/AnnalsATS.201701-042AW.

40. Cheng Z, Almeida FA. Mitochondrial alteration in type 2 diabetes and obesity: an epigenetic link. *Cell Cycle* 2014;13:890–897. doi:10.4161/cc.28189.

39. Koves TR, Ussher JR, Noland RC, et al. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab* 2008;7:45–56. doi:10.1016/j.cmet.2007.10.013.

38. Stuhlunger MC, Stanger O. Asymmetric dimethyl-L-arginine (ADMA): a possible link between homocyst(e)ine and endothelial dysfunction. *Curr Drug Metab* 2005;6:3–14. doi:10.2174/1389200052997393.

37. Bayani MA, Milara J, Estornut C, Cortijo J. Nitric oxide system and bronchial epithelium: more than a barrier. *Front Physiol* 2021;12:687381. PMID: 34276407; PMCID: PMC8279772. doi:10.3389/fphys.2021.687381.

36. Holguin F, Comhair SAA, Hazen SL, et al. An association between L-arginine/asymmetric dimethyl arginine balance, obesity, and the age of asthma onset phenotype. *Am J Respir Crit Care Med* 2013;187:153–159. doi:10.1164/rccm.201210-12700C.

35. Grasmann H, Holguin F. Oxidative stress and obesity-related asthma. *Paediatr Respir Rev* 2021;37:18–21. PMID: 32660723. doi:10.1016/j.prrv.2020.05.004.

34. Konra’ Dova’ V, Copova’ C, Sukova’ B, Houštěk J. Ultrastructure of the bronchial epithelium in three children with asthma. *Pediatr Pulmonol* 1985;1:182–187. doi:10.1002/ppul.1950010403.
81. Mabalirajan U, Dinda AK, Kumar S, et al. Mitochondrial structural changes and dysfunction are associated with experimental allergic asthma. J Immunol. 2008;181:3540–3548. doi:10.4049/jimmunol.181.5.3540

82. Aguiler-Aguirre L, Bacsi A, Saavedra-Molina A, Kurosky A, Sur S, Boldogh I. Mitochondrial dysfunction increases allergic airway inflammation. J Immunol. 2009;183:5379–5387. doi:10.4049/jimmunol.0900228

83. Ahmad T, Kumar M, Mabalirajan U, et al. Hypoxia response in asthma: differential modulation on inflammation and epithelial injury. Am J Respir Cell Mol Biol. 2012;47:1–10. doi:10.1165/rcmb.2011-0203OC

84. Winnica D, Corey C, Mullett S, et al. Bioenergetic differences in the airway epithelium of lean versus obese asthmatics are driven by nitric oxide and reflected in circulating platelets. Antioxid Redox Signal. 2019;3(10):673–686. doi:10.1089/ars.2018.7627

85. Komakula S, Khatri S, Mermis I, et al. Body mass index is associated with reduced exhaled nitric oxide and higher exhaled 8-isoprostan in asthmatics. Respir Med. 2007;68(8):32. doi:10.11015/1426-9281-9-32

86. Aldakheel FM, Thomas PS, Bourke JE, Matheson MC, Dharmage SC, Lowe AJ. Relationships between adult asthma and oxidative stress markers and pH in exhaled breath condensate: a systematic review. Allergy. 2016;71(6):741–757. doi:10.1111/all.12865

87. Mabalirajan U, Rehman R, Ahmad T, et al. Linoleic acid metabolite drives severe asthma by causing airway epithelial injury. Sci Rep. 2013;3(1). doi:10.1038/srep01349

88. Holguin F, Khatri S, Serpio E, Powers RW, Trudeau J, Wenzel SE. Reduced L-arginine/ADMA as a potential mechanism to explain increased symptom severity and reduced atopy in late onset obese asthmatics. Am J Respir Crit Care Med. 2012;185:A2197.

89. Brown SD, Baxter KM, Stephenson ST, Esper AM, Brown LA, Fitzpatrick AM. Airway TGF-β1 and oxidant stress in children with severe asthma: association with airflow limitation. J Allergy Clin Immunol. 2012;129(2):388–396, e1–8. PMID: 22206775; PMCID: PMC3268912. doi:10.1016/j.jaci.2011.11.037

90. Holguin F. Arginine and nitric oxide pathways in obesity-associated asthma. J Allergy (Cairo). 2013;71:4595. PMID: 23710196; PMCID: PMC3654368. doi:10.1153/2013/714595

91. Wu W, Bang S, Bleeker ER, et al. Multiview cluster analysis identifies variable corticosteroid response phenotypes in severe asthma. Am J Respir Crit Care Med. 2019;199(1):1358–1367. doi:10.1164/rcrm.201808-1543OC

92. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. Lancet. 2009;373(9678):1905–1917. doi:10.1016/S0140-6736(09)60263-6

93. Lu KD, Breyssse PN, Diette GB, et al. Being overweight increases susceptibility to indoor pollutants among urban children with asthma. J Allergy Clin Immunol. 2013;131:1017–1023, 1023.e1–1023.e3. doi:10.1016/j.jaci.2012.12.1570

94. Alexeeff SE, Litonjua AA, Suh H, Sparrow D, Vokonas PS, Schwartz J. Ozone exposure and lung function: effect modified by obesity and airways hypersensitiveness in the VA normative aging study. Chest. 2007;132:1890–1897. doi:10.1378/chest.07-1126

95. Arrieta MC, Finlay B. The intestinal microbiota and allergic asthma. Curr Opin Allergy Clin Immunol. 2013;13(4):341–347. doi:10.1097/MCI.0b013e328363d751

96. Tavares da Silva S, Araújo Dos Santos C, Bressan J. Intestinal microbiota; relevance to obesity and modulation by prebiotics and probiotics. Nutrição Hospitalar. 2014;28(4):1039–1048. doi:10.5305/nh.2014.28.4.6525

97. Ley RE. Obesity and the human microbiome. Curr Opin Gastroenterol. 2010;26:5–11. doi:10.1097/MOG.0b013e3283233d75

98. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444:1022–1023. doi:10.1038/nature05224

99. Arrieta MC, Finlay B. The intestinal microbiota and allergic asthma. J Infect. 2014;69(Suppl1):S53e5. doi:10.1016/j.jinf.2014.07.015

100. Ygenteruan Y, Ran N, Xiong L, et al. Obesity-related asthma: immune regulation and potential targeted therapies. J Immunol Res. 2018:2018:1943497. PMID: 30050954; PMCID: PMC6046139. doi:10.1158/2018:1943497

101. Arrieta MC, Finlay B. The intestinal microbiota and allergic asthma. J Infect. 2014;69(Suppl1):S53e5. doi:10.1016/j.jinf.2014.07.015

102. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444:1022–1023. doi:10.1038/nature05224

103. Catrysse L, van Loo G. Inflammation and the metabolic syndrome: the tissue-specific functions of NF-κB. Trends Cell Biol. 2017;27(6):417–429. doi:10.1016/j.tcb.2017.01.006

104. Cami PD, Bibiloni R, Knauf C, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008;57(6):1470–1481. PMID: 18305141. doi:10.2337/db07-1403

105. Michalovich D, Rodriguez-Perez N, Smolinska S, et al. Obesity and disease severity magnify disturbed microbiome-immune interactions in asthma patients. Nat Commun. 2019;10:1–14. doi:10.1038/s41467-018-07882-8

106. Huang YJ, Nariya S, Breysse PN, Diette GB, et al. Being overweight increases susceptibility to indoor pollutants among urban children with asthma. J Allergy Clin Immunol. 2013;131:1017–1023, 1023.e1–1023.e3. doi:10.1016/j.jaci.2012.12.1570

107. Mabalirajan U, Rehman R, Ahmad T, et al. Linoleic acid metabolite drives severe asthma by causing airway epithelial injury. Sci Rep. 2013;3(1). doi:10.1038/srep01349

108. Holguin F, Khatri S, Serpio E, Powers RW, Trudeau J, Wenzel SE. Reduced L-arginine/ADMA as a potential mechanism to explain increased symptom severity and reduced atopy in late onset obese asthmatics. Am J Respir Crit Care Med. 2012;185:A2197.

109. Brown SD, Baxter KM, Stephenson ST, Esper AM, Brown LA, Fitzpatrick AM. Airway TGF-β1 and oxidant stress in children with severe asthma: association with airflow limitation. J Allergy Clin Immunol. 2012;129(2):388–396, e1–8. PMID: 22206775; PMCID: PMC3268912. doi:10.1016/j.jaci.2011.11.037

110. Huang YJ, Nariya S, Harris JM, et al. The airway microbiome in patients with severe asthma: associations with disease features and severity. J Allergy Clin Immunol. 2015;136:874e8. doi:10.1016/j.jaci.2015.05.044

111. Wood LG, Garg ML, Gibson PG. A high-fat-challenge increases airway inflammation and impairs bronchodilator recovery in asthma. J Allergy Clin Immunol. 2011;127:1133–1140. doi:10.1016/j.jaci.2011.01.036

112. Soular A, Seaton A, Brown K. Bronchial reactivity and dietary antioxidants. Thorax. 1997;52:166–170. doi:10.1136/thx.52.2.166

113. Kien CL, Bunn JY, Fukagawa NK, et al. Lipidomic evidence that lowering the typical dietary palmitate to oleate ratio in humans decreases the leukocyte production of proinflammatory cytokines and muscle expression of redox-sensitive genes. J Nutr Biochem. 2015;26:1599–1606. doi:10.1016/j.jnutbio.2015.07.014
114. Singh VP, Aggarwal R, Singh S, et al. Metabolic syndrome is associated with increased o xo-nitrative stress and asthma-like changes in lungs. PLoS One. 2015;10:e0129850. doi:10.1371/journal.pone.0129850

115. Tashiro H, Shore SA. Obesity and severe asthma. Allergol Int. 2019;68(2):135–142. PMID: 30509734; PMCID: PMC6540088. doi:10.1016/j.aili.2018.10.004

116. Wood LG, Li Q, Scott HA, et al. Saturated fatty acids, obesity, and the nucleotide oligomerization domain-like receptor protein 3 (NLRP3) inflammasome in asthmatic patients. J Allergy Clin Immunol. 2019;143:305e15. doi:10.1016/j.jaci.2018.04.037

117. Wood LG, Garg ML, Smart JM, Scott HA, Barker D, Gibson P. Manipulating antioxidant intake in asthma: a randomized controlled trial. Am J Clin Nutr. 2012;96:534–543. doi:10.3945/ajcn.111.023263.

118. Wood LG, Garg ML, Powell H, Gibson PG. Lycopene-rich treatments modify nonoeosinophilic airway inflammation in asthma: proof of concept. Free Radic res. 2008;42:94–102. doi:10.1080/107157607017567307

119. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev. 2015;16:341e9. doi:10.1111/obr.12239

120. Martineau AR, MacLaughlin BD, Hooper RL, et al. Double-blind randomised placebo-controlled trial of bolus-dose vitamin D3 supplementation in adults with asthma (ViDiAs). Thorax. 2015;70:451e6.

121. Aydin M, Koca C, Ozol D, et al. Interaction of metabolic syndrome with asthma in premenopausal women: role of adipokines. Inflammation. 2013;36:1232–1238. doi:10.1007/s10753-013-9660-9

122. van Huisstede A, Cabezas MC, Birnie E, et al. Systemic inflammation and lung function impairment in morbidly obese subjects with the metabolic syndrome. J Obes. 2013;2013:131349. PMID: 23509614; PMCID: PMC3595660. doi:10.1155/2013/131349

123. Forno E, Han -Y-Y, Muzumdar RH, Celedón JC. Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma. J Allergy Clin Immunol. 2015;136(2):304–311.e8. doi:10.1016/j.jaci.2015.01.010

124. Forno E, Zhang P, Nouraie M, et al. The impact of bariatric surgery on asthma control differs among obese individuals with reported prior or current asthma, with or without metabolic syndrome. PLoS One. 2019;14(4):e0214730. doi:10.1371/journal.pone.0214730.

125. Nie Z, Jacoby DB, Fryer AD. Hyperinsulinemia potentiates airway responsiveness to parasympathetic nerve stimulation in obese rats. Am J Respir Cell Mol Biol. 2014;51:251–261. doi:10.1165/rcmb.2013-0452OC

126. Leiria LO, Arantes-Costa FM, Calixto MC, et al. Increased airway reactivity and hyperinsulinemia in obese mice are linked by ERK signaling in brain stem cholinergic neurons. Cell Rep. 2015;11:934–943. doi:10.1016/j.celrep.2015.04.012

127. Thomsen SF, Ulrik CS, K yvik KO, et al. Association between obesity and asthma in a twin cohort. Allergy. 2007;62(10):1199–1204. PMID: 17845591. doi:10.1111/j.1398-9995.2007.01480.x

128. Murphy A, Tantisira KG, Soto-Quiros ME, et al. PRKCA: a positional candidate gene for body mass index and asthma. Am J Hum Genet. 2009;85(1):87–96. PMID: 19576566; PMCID: PMC2706964. doi:10.1086/ahr.2009.06.011

129. Castro-Giner F, Korgevins M, Imboden M, et al. Joint effect of obesity and TNFAvariability on asthma: two international cohort studies. Eur Respir J. 2009;33:1003–1009. PMID: 19196817. doi:10.1183/09031936.00410608

130. González JR, Cáceres A, Esco T, et al. A common 16p11.2 inversion underlies the joint susceptibility to asthma and obesity. J Clin Invest. 2009;119(9):3503–3505 e3. doi:10.1172/jci35033

131. Cloutier MM, Baptista AP, Blake KV, Expert Panel Working Group of the National Heart L, Blood Institute a, coordinated National Asthma E. Focused updates to the asthma management guidelines: a report from the national asthma education and prevention program coordinating committee expert panel working group. J Allergy Clin Immunol. 2020;146(6):1217–1270. doi:10.1016/j.jaci.2020.10.003

132. Peerboom S, Graff S, Seidel L, et al. Predictors of a good response to inhaled corticosteroids in obesity-associated asthma. Biochem Pharmacol. 2020;179:113994. doi:10.1016/j.bcp.2020.113994

133. Tashiro H, Takahashi K, Sadamatsu H, et al. Biomarkers for overweight in adult-onset asthma. J Asthma Allergy. 2020;9(9):3503–3505 e3. doi:10.2147/JAA.S276371

134. Camargo CA Jr, Boulet LP, Sutherland ER, et al. Body mass index and response to asthma therapy: fluticasone propionate/salmeterol versus montelukast. J Asthma. 2010;47(1):76–82. doi:10.3109/02770909033838494

135. Thompson CA, Eslick SR, Berthon BS, Wood LG. Body mass in obese and healthy weight asthma: systematic review/ meta-analysis. Eur Respir J. 2021;57(3):2000612. doi:10.1183/13993003.00612-2020

136. Luthe SK, Hirayama A, Goto T, Faridi MK, Camargo CA Jr, Hasegawa K. Association between obesity and acute severity among patients hospitalized for exacerbation. J Allergy Clin Immunol Pract. 2018;6(9):1936–1941 e4. doi:10.1016/j.jcip.2018.02.001

137. Ilmarinen P, Vahatalo I, Tumonisto LE, Niemela O, Kankaanranta H. Long-term adherence to inhaled corticosteroids in clinical phenotypes of adult-onset asthma. J Allergy Clin Immunol Pract. 2021;9(9):3503–3505 e3. doi:10.1016/j.jcip.2021.04.057

138. Lefauudex D, De Meulder B, Loza MJ, et al. U-BIOPRED clinical adult asthma clusters linked to a subset of sputum omics. J Allergy Clin Immunol. 2020;136(6):1797–1807. doi:10.1016/j.jaci.2020.08.048

139. Sutherland ER, Lehrman EB, Teoderescu M, Wechsler ME, National Heart L, Blood Institute a, Clinical Research Network. Body mass index and phenotype in mild-to-moderate persistent asthma. J Allergy Clin Immunol. 2009;123(6):1328–34 e1. doi:10.1016/j.jaci.2009.04.005

140. Peters-Golder M, Swann A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. Eur Respir J. 2006;27(3):495–503. doi:10.1183/09031936.00077205

141. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. Respir Med. 2007;101(11):2240–2247. doi:10.1016/j.rmed.2007.06.031

142. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DY. Body mass and glucocorticoid response in asthma. Am J Respir Crit Care Med. 2008;178(7):682–687. doi:10.1164/rcrm.200801-076OC

143. Al Heialy S, Gaudet M, Ramakrishnan RK, et al. Contribution of IL-17 in steroid hyporesponsiveness in obese asthmatics through dysregulation of glucocorticoid receptors alpha and beta. Front Immunol. 2020;11:1724. doi:10.3389/fimmu.2020.01724

144. Demarche SF, Schleich FN, Henket MA, Paulus VA, Van Hees TJ, Louis RE. Effectiveness of inhaled corticosteroids in real life on clinical outcomes, sputum cells and systemic inflammation in asthmatics: a retrospective cohort study in a secondary care centre. BMJ Open. 2017;7(11):e018186. doi:10.1136/bmjopen-2017-018186
145. Yadav UC, Srivastava SK. Cysteinyl leukotrienes (CysLTs): role in obesity-induced asthma. *Curr Mol Med*. 2015;15(7):598–605. doi:10.2174/156652401566150831130954

146. Farzan S, Khan S, Elera C, Tsang J, Akerman M, DeVoti J. Effectiveness of montelukast in overweight and obese atopic asthmatics. *Ann Allergy Asthma Immunol*. 2017;119(2):189–190. doi:10.1016/j.anai.2017.05.024

147. Sutherland ER, Camargo CA Jr, Busse WW, et al. Comparative effect of body mass index on response to asthma controller therapy. *Allergy Asthma Proc*. 2010;31(1):20–25. doi:10.2500/aap.2010.31.3307

148. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384(19):1800–1809. PMID: 33979488. doi:10.1056/NEJMoa2034975

149. Saeed MA, Gribben KC, Alam M, Lyden ER, Hanson CK, LeVan TD. Association of dietary fiber on asthma, respiratory symptoms, and systemic immunity to alleviate obesity syndrome in the adult national health and nutrition examination survey population. *Ann Am Thorac Soc*. 2020;17(9):1062–1068. PMID: 32369709. doi:10.1513/AnnalsATS.201910-7760C

150. Gutkowski P, Madalinski K, Gurek M, Dmenska H, Michalkiewicz J. Effect of orally administered probiotic strains “Lactobacillus” and “Bifidobacterium” in children with atopic asthma. *Central-Eur J Immunol*. 2010;58:2004605. doi:10.1183/13993003.0460-2020

151. Holguin F, Grasemann H, Sharma S, et al. L-Citrulline increases nitric oxide and improves control in obese asthmatics. *Pediatr Pulmonol*. 2010;45(11):1111–1120. PMID: 20658483. doi:10.1002/ppul.21296

152. Inam M, Sreenivasan T, Franks H, et al. L-Citrulline increases nitric oxide and improves control in obese asthmatics. *JCI Insight*. 2019;4(24):e131733. PMID: 31714895; PMCID: PMC6975256. doi:10.1172/jci.insight.131733

153. Upala S, Thavaraputta S, Sanguankeo A. Improvement in pulmonary function in asthmatic patients after bariatric surgery: a systematic review and meta-analysis. *Exerc Sport Sci Rev*. 2018;46(4):136–1376. doi:10.1249/RESS.0000000000000157

154. Freitas PD, Silva AG, Ferreira PG, et al. Exercise improves physical activity and comorbidities in obese adults with asthma. *J Sci Med Sport*. 2016;19(7):1062–1068. PMID: 27174895. doi:10.1016/j.jsams.2015.09.002

155. Park J, Kang W, Lee J, et al. Effects of weight loss lead to reversibility of asthma? *Asthma Proc*. 2015;31(4):1810–1832. doi:10.1016/j.asthamp.2015.08.007

156. Lim R. Bariatric procedures for the management of severe obesity: descriptions. In: Post TW, editor. *UpToDate*; 2019. doi:10.1168/12931-021-01746-4

157. Pakhale S, Baron J, Dent R, Vandemheen K, Aaron SD. Effects of weight loss on airway responsiveness in obese adults with asthma: does weight loss lead to reversibility of asthma? *Chest*. 2015;147:1582e90. doi:10.1378/chest.14-3105

158. Özbey Ü, Balaban S, Sözener ZÇ, Uçar A, Mungan D, Mısırlıgil Z. The effect of diet-induced weight loss on asthma control and quality of life in obese adults with asthma: a randomized, placebo-controlled trial. *Eur J Clin Nutr*. 2019;52:78–85. doi:10.1038/s41430-018-01026-6

159. Pahuja S, Bakhshi S, Pradhan A, Haider S, et al. Impact of baseline patient characteristics on dupilumab efficacy in type 2 asthma. *Eur Respir J*. 2021;58:2004605. doi:10.1183/13993003.0460-2020

160. Özbey Ü, Balaban S, Sözener ZÇ, Uçar A, Mungan D, Mısırlıgil Z. The effect of diet-induced weight loss on asthma control and quality of life in obese adults with asthma: a randomized, placebo-controlled trial. *Ann Allergy Asthma Immunol*. 2010;104(1):1–12. doi:10.1016/j.anai.2009.09.003

161. Stoodley I, Williams L, Thompson C, Scott H, Wood L. Evidence for lifestyle interventions in asthma. *Breathe*. 2019;15(2):e50–e61. doi:10.1183/20734735.0019-2019

162. Upadhyaya S, Baron J, Dent R, Vanderheiden K, Aaron SD. Effects of weight loss on airway responsiveness in obese adults with asthma: does weight loss lead to reversibility of asthma? *Chest*. 2015;147:1588e90. doi:10.1378/chest.14-3105

163. Saeed MA, Gribben KC, Alam M, Lyden ER, Hanson CK, LeVan TD. Association of dietary fiber on asthma, respiratory symptoms, and inflammation in the adult national health and nutrition examination survey population. *Ann Am Thorac Soc*. 2020;17(9):1062–1068. PMID: 32369709. doi:10.1513/AnnalsATS.201910-7760C

164. Gutkowski P, Madalinski K, Gurek M, Dmenska H, Michalkiewicz J. Effect of orally administered probiotic strains “Lactobacillus” and “Bifidobacterium” in children with atopic asthma. *Central-Eur J Immunol*. 2010;58:2004605. doi:10.1183/13993003.0460-2020

165. Holguin F, Grasemann H, Sharma S, et al. L-Citrulline increases nitric oxide and improves control in obese asthmatics. *JCI Insight*. 2019;4(24):e131733. PMID: 31714895; PMCID: PMC6975256. doi:10.1172/jci.insight.131733

166. Updike PD, Silva AG, Ferreira PG, et al. Exercise improves physical activity and comorbidities in obese adults with asthma. *Med Sci Sports Exerc*. 2018;50(7):1367–1376. doi:10.1249/MSS.0000000000000157

167. Lim R. Bariatric procedures for the management of severe obesity: descriptions. In: Post TW, editor. *UpToDate*. UpToDate; 2021.

168. Updike PD, Silva AG, Ferreira PG, et al. Exercise improves physical activity and comorbidities in obese adults with asthma. *Med Sci Sports Exerc*. 2018;50(7):1367–1376. doi:10.1249/MSS.0000000000000157

169. Nyenhuis SM, Dixon AE, Obi AK, et al. Impact of lifestyle interventions targeting healthy diet, physical activity, and weight loss on asthma in adults: what is the evidence? *J Allergy Clin Immunol Pract*. 2018;6(3):751–763. doi:10.1016/j.jaip.2017.10.026