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Obesity and severe asthma

Hiroki Tashiro, Stephanie A. Shore*

Department of Environmental Health, Harvard University T.H. Chan School of Public Health, Boston, MA, USA

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ABSTRACT

Obesity is an important global health issue for both children and adults. Obesity increases the prevalence and incidence of asthma and also increases the risk for severe asthma. Here we describe the features of severe asthma phenotypes for which obesity is a defining characteristic, including steroid resistance, airway inflammation, and co-morbidities. We also review current concepts regarding the mechanistic basis for the impact of obesity in severe asthma, including possible roles for vitamin D deficiency, systemic inflammation, and the microbiome. Finally, we describe data indicating a role for diet, weight loss, and exercise in the treatment of severe asthma with obesity. Better understanding of the mechanistic basis for the role of obesity in severe asthma could lead to new therapeutic options for this population.

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Introduction

Severe asthma is an important clinical issue that accounts for approximately 10% of all of asthma patients but 60% of the medical costs of asthma.^{1–3} Severe asthma is asthma that is uncontrolled even though the patient is on systemic corticosteroids or high dose inhaled corticosteroids plus another controller medication.³ Obesity is among the factors that increase the risk for severe asthma. The purpose of this article is to review the data supporting a relationship between obesity and asthma, to discuss the data indicating that obesity increases the severity of asthma, to present the clinical characteristics of severe asthmatics who are obese, and to explore potential mechanisms that may account for the impact of obesity on severe asthma, including data from animal models. Understanding the mechanistic basis for the impact of obesity on severe asthma may lead to new therapeutic options for this population in whom standard asthma therapeutics are relatively ineffective.

Obesity: a risk factor for asthma

Obesity is a global health issue for both children and adults. The World Health Organization (WHO) reported that between 1975 and 2016 the worldwide prevalence of obesity nearly tripled so that by

2016, 39% of adults worldwide were overweight and 13% were obese. The prevalence of overweight and obesity among children and adolescents rose from 4% to 18% over the same time interval.^{4,5} In the U.S., approximately 17% of children (2–19 years old) and 35% of adults are currently obese, with lower obesity prevalences in Asians (approximately 9% in children and 11% in adults).⁴ By 2030, U.S. adult obesity prevalence is expected to reach 51%.⁶ In Japan, the prevalence of overweight and obesity has not increased as rapidly. In 2014, overweight and obesity prevalences were approximately 21% and 4%, respectively, in Japanese adults.⁷

Obesity is a risk factor for a number of common life-threatening conditions including atherosclerosis, hypertension, and type 2 diabetes. Obesity also increases the risk for asthma.⁸ Epidemiological data indicate that asthma is more common in obese than lean subjects. For example, in the U.S., asthma is approximately twice as prevalent in obese as in lean adults.⁹ In Japanese patients, the odds ratio for asthma prevalence in obese versus lean subjects is 3.31 for males and 3.02 for females.^{10,11} This association between obesity and asthma is observed in most ethnic groups, across all age groups, and in both sexes,¹² although some studies have noted greater effect sizes in females than in males.^{13–15} The relationship also appears stronger for those with central versus general adiposity.^{16–19} For example, a large (>88,000 women) study from the California Teachers Study cohort reported that increased waist circumference was associated with asthma even among those with BMI's in the normal range.¹⁶ Atopic status also appears to have an impact on the magnitude of the obesity–asthma relationship. In a study from Australia involving 4060 patients with asthma,

* Corresponding author. Molecular and Integrative Physiological Sciences Program, Department of Environmental Health, Harvard University T.H. Chan School of Public Health, 665 Huntington Avenue 1–319, Boston, MA 02115, USA.

E-mail address: sshore@hsph.harvard.edu (S.A. Shore).

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stratification of the study population by atopic status identified an association between obesity and asthma only in the non-atopic population.¹⁷ Similar results were obtained in an adult study population from Southern Sweden¹⁸ and among children and adolescents who were participants in the National Health and Nutrition Examination Survey (NHANES),^{15,20} although the results are not consistent.¹⁵ Given the key importance of atopy as a risk factor for asthma, it may be difficult to observe the additional impact of obesity in atopic subjects.

The first published prospective analysis of the relationship between obesity and asthma reported data from almost 86,000 women who participated in the Nurses Health Study.¹⁴ Women who were initially asthma-free were followed for 4 years during which time some of the women received a physician's diagnosis of asthma. Initial BMI was strongly associated with risk for new onset asthma, with a relative risk of 2.6 for obese subjects even after adjustment for a number of factors including age, smoking history, and physical activity. There was also a clear dose-response relationship between BMI and risk of new-onset asthma. While this study involved only women, an even larger prospective study from Norway, published shortly thereafter, indicated a similar relationship between BMI and new onset asthma in men.²¹ Since that time, many additional prospective studies have been performed with virtually all indicating an increased risk for incident asthma in obese and overweight adults.⁹ Similar results are obtained in children. For example, meta-analysis of data from prospective studies in children followed for at least one year after BMI assessment indicated a relative risk ratio of 1.5 for obesity and incident asthma, with significant effects in both boys and girls,²² though another meta analysis indicated a greater relative risk in boys than girls.²³ A recent study from the Boston Birth Cohort, which followed children from birth, reported that early life rapid weight gain was associated with an increased risk of asthma.²⁴ Taken together, the data indicate that obesity antedates and may therefore contribute to the development of asthma.

A recent report from the Southern California Children's Health Study suggests that asthma may also lead to obesity.²⁵ The authors followed more than 2000 initially non obese children for up to 10 years. Children with an initial diagnosis of asthma were approximately 50% more likely to become obese than children without asthma. Interestingly, the analysis also indicated that the increased risk of obesity with asthma was driven by children who were already overweight at baseline, whereas there was no increased risk of obesity in those asthmatic children who were of normal weight at baseline. Since overweight is itself a very strong predictor of subsequent obesity, it is important to consider the possibility that overweight was driving both initial asthma and subsequent obesity, and that the two phenotypes, obesity and asthma, interact with each other in multiple complex ways. Such interactions may be further complicated in the setting of prolonged systemic corticosteroid therapy for severe asthma, since such therapy can itself induce weight gain.

Obesity increases the severity of asthma

Obesity is extremely common in patients with severe asthma. In the TENOR study of severe asthmatics, approximately 31% and 57% of children and adults with severe asthma are obese, compared to obesity rates of 20% and 35% in children and adults within the general US population.²⁶ Similarly in the British Thoracic Society Difficult Asthma Registry, approximately 48% of adult severe asthmatics are obese compared to an adult obesity rate of approximately 25% in the general British adult population.²⁷ While some of this increased prevalence of obesity within the severe asthma population may reflect the obesogenic effects of the systemic

corticosteroids that are widely used in this population, there is also evidence that obesity increases the severity of asthma. For example, in the Portuguese National Health Survey of over 30,000 individuals, overweight (25.0–29.9 kg/m²), class I obesity (30.0–34.9 kg/m²), class II obesity (35.0–39.9 kg/m²), and class III obesity (≥ 40.0 kg/m²) were associated with odds ratios (OR) for severe asthma (defined as an emergency room visit for asthma within the last 12 months) of 1.36, 1.50, and 3.70, respectively.²⁸ Similarly, in a study of almost 30,000 U.S. adults and children with persistent asthma, higher body mass index (BMI) was associated with increased risk of asthma exacerbations, defined as oral corticosteroid dispensings linked to an asthma encounter.²⁹ In the U.S., obese adults are at higher risk of hospitalization for asthma than lean adults³⁰ and in those hospitalized for asthma exacerbations, obesity is associated with a significantly higher risk for mechanical ventilation use and longer hospitalization stays.^{31,32} Similarly, a Japanese study of almost 40,000 asthmatic children identified from inpatient records, noted that obesity was associated with significantly longer hospital stays and greater likelihood of 30-day readmission.³³ Notably, compared to normal weight asthmatics presenting to emergency rooms with severe exacerbations, obese asthmatics had higher rates of inhaled steroid and theophylline use in the week prior to their ER visit, suggesting poorer efficacy of these medications.³²

Clinical characteristics of obese severe asthmatics

The etiology of asthma symptoms is highly heterogeneous, resulting in a variety of asthma phenotypes. In 2008, Haldar *et al.*³⁴ applied the statistical tools of cluster analysis for the first time to data from a large cohort of asthmatics and characterized several asthma phenotypes. In the decade since, substantial effort has focused on such asthma phenotyping since it has the power to identify patients that may respond well to certain therapeutics. Among the various asthma clusters identified by Haldar *et al.* was a group with "obese asthma". These patients had a particular set of characteristics that included late onset of asthma, predominantly female sex, high level of symptoms, low sputum eosinophils, low atopy, moderate airway hyperresponsiveness and reversibility of obstruction, and low responsiveness to inhaled corticosteroids³⁴. A few years later, the same technique was applied to asthma patients in the U.S. Severe Asthma Research Program (SARP).³⁵ In the patients with severe asthma, the authors again identified a cluster that were predominantly obese, and had late-onset asthma, relatively low atopy, and substantially lower lung function compared to the other asthmatics in the cohort. Subsequently, others expanded the phenotyping of obese asthmatics and identified, both in severe and non-severe asthmatics, at least two obese asthma phenotypes.^{36–38} One group included patients with early-onset asthma usually triggered by allergens, with eosinophilia and high serum IgE titers, but exacerbated by obesity. The other group included patients with late, usually adult-onset asthma, who were predominantly female and lacked Th2 markers.³⁸ As described above, in this latter group, airway hyperresponsiveness, a defining feature of asthma, was reversed following weight loss, suggesting that obesity was causal for their asthma.³⁶

Corticosteroid responsiveness

Steroids are less effective in obese than in lean subjects with asthma.³⁹ Boulet *et al.*⁴⁰ reported the results of administering inhaled fluticasone with or without the long acting β_2 -agonist, salmeterol, to over 1000 asthmatics who were initially not taking corticosteroids. Compared to subjects with normal BMI's, obese subjects, especially those with marked obesity, had a reduced odds of achieving asthma control. Part of this reduced efficacy of

corticosteroids in obese asthmatics may be related to obesity-related changes in the anti-inflammatory effects of these agents. The ability of dexamethasone to induce MKP-1, a glucocorticoid responsive gene, in peripheral blood mononuclear cells and in bronchoalveolar lavage cells is reduced in obese versus lean asthmatics.⁴¹ Notably, this effect of obesity was only observed in asthmatics and not in healthy controls. Indeed, in severe asthmatics with type2-high asthma who are obese, many continue to have high expression of type 2 cytokine-dependent gene expression in sputum cells, despite inhaled corticosteroid use.⁴² While these studies indicate that obesity does indeed reduce the response to steroids, there may be an important additional reason why obese asthmatics do not respond well to these agents: steroids target the immune processes that mediate allergic responses, but many obese subjects with severe asthma are non-atopic.^{43–45}

Airway inflammation

Elevations in sputum neutrophils are common in severe asthma and neutrophils are proposed to contribute to the etiology of the disease in some severe asthmatics.^{46,47} Several clinical studies have evaluated airway inflammation in the setting of severe or uncontrolled asthma with obesity. Collectively, the data support the hypothesis that obesity seems to polarize asthma patients towards a neutrophil dominant rather than eosinophil dominant inflammatory phenotype. For example, Scott *et al.*⁴⁸ analyzed induced sputum from obese and non obese asthmatic patients. Sputum neutrophils but not eosinophils were higher in obese asthma than non-obese, though the relationship was only significant in the female patients. Similarly, Marijse *et al.*⁴⁹ also reported greater sputum neutrophils but not eosinophils in obese versus lean subjects with poorly controlled asthma. These authors and others⁵⁰ also reported greater sputum IL-17A, a cytokine important for neutrophil recruitment, in the obese than the lean patients suggesting that this cytokine may be contributing the neutrophil recruitment in these patients. Data from animal models also suggest a link between IL-17A and obese asthma.⁵¹ Obese mice typically exhibit innate airway hyperresponsiveness, but this hyperresponsiveness is not observed if the animals are IL-17A deficient.⁵² Compared to lean mice, obese mice also have greater responses to ozone, a common asthma trigger that promotes neutrophil recruitment to the airways, including greater ozone-induced airway hyperresponsiveness, an effect that is attenuated by blocking IL-17A.⁵³

Even though most studies indicate reduced sputum eosinophils in obese versus lean subjects with asthma, submucosal eosinophils are elevated in obese versus lean severe asthmatics.⁵⁴ IL-5, an eosinophil survival factor, is also elevated in sputum of obese versus lean severe asthmatics.^{49,54} Thus, it is unlikely that eosinophils fail to survive within the airway lumens of obese asthmatics. Instead, the data suggest that the eosinophils fail to migrate from the tissues into the airways. Thus, some severe obese asthmatics may have a Th2 dominant type of asthma, as described above, and may benefit from eosinophil targeted therapeutics.

Co-morbidities

Aside from asthma, obese subjects may have several other comorbid conditions including gastroesophageal reflux disease (GERD), hypertension, obstructive sleep apnea, insulin resistance, and dyslipidemia. These conditions may complicate asthma in the obese and there is evidence that at least some of these comorbidities may contribute to severe obese asthma. For example, GERD is very common in severe asthma,^{55,56} especially in patients who are obese²⁷ and in SARP, subjects in the obese asthma clusters

have more GERD than subjects in the other severe asthma clusters.³⁵ Reflux can cause bronchoconstriction,⁵⁷ and GERD is an important risk factor for asthma exacerbations in patients with severe asthma.^{58,59} Several large randomized placebo controlled clinical trials have evaluated the ability of proton pump inhibitors to ameliorate asthma symptoms, but most identified only a modest effect or no effect of treatment, although none of the studies focused specifically on obese asthmatics.⁶⁰

There is also a high prevalence of obstructive sleep apnea (OSA) in patients with severe asthma^{61,62} with rates as high as 80%, and the frequency of severe asthma exacerbations is higher in asthmatics with OSA than those without OSA.⁶³ In SARP, subjects with high risk for OSA had more asthma symptoms and more β_2 -agonist use than those with low OSA risk.⁶⁴ Importantly, these subjects had greater sputum neutrophils, consistent with the link between sputum neutrophils and severe asthma described above. OSA is associated with systemic inflammation,⁶⁵ and in the obese, the intermittent hypoxemia associated with repeated obstructive episodes may exacerbate already existing adipose tissue hypoxia, worsening adipocyte death, macrophage infiltration, and consequent systemic inflammation characteristic of obesity (see below). There is evidence that continuous positive airway pressure (CPAP), a treatment for OSA, reduces systemic inflammation in asthmatics and also reduces airway responsiveness, asthma symptoms, and β_2 -agonist use.^{60,66} Bariatric surgery also improves both asthma and OSA.⁶⁷

Type 2 diabetes is also major complication of obesity and there is some evidence that obesity coupled with insulin resistance may interact to promote asthma. Cardet *et al.* analyzed data from 12,421 adult subjects who participated in NHANES. The authors observed a strong association between obesity and current asthma, as expected, but this relationship was stronger in patients in the highest than the lowest tertile of insulin resistance.⁶⁸ Insulin resistance also amplifies reductions in lung function in overweight or obese adolescents.^{69,70} Exactly how insulin resistance might promote asthma in the obese has not been established, but there is evidence of effects of insulin both on the immune system and on airway smooth muscle.^{71,72} A retrospective analysis of data from 1332 patients with asthma and diabetes indicated lower risk of asthma hospitalization in patients who were taking metformin for treatment of their diabetes than in those who were not.⁷³ However, a randomized controlled trial of treatment with another type 2 diabetes therapeutic, pioglitazone, indicated little benefit in obese asthmatics. Moreover, pioglitazone treatment caused additional weight gain in these patients.⁷⁴

Mechanistic basis for the role of obesity in severe asthma

Many other factors may contribute to the ability of obesity to exacerbate asthma. Below we discuss several of these, including the potential role for obesity-related changes in the microbiome.

Vitamin D deficiency

Obesity and overweight are associated with vitamin D deficiency,^{75–77} likely as a result of sequestration of this fat soluble vitamin in adipose tissue. A meta-analysis of observational studies evaluating vitamin D deficiency and anthropometric measures indicates that vitamin D deficiency is 35% and 24% higher in obese and overweight subjects, respectively, than in normal weight subjects.⁷⁸ The effects of vitamin D on bone health are well established, and there is increasing evidence of a role for vitamin D in blood pressure and immune system regulation. There is also some evidence that the vitamin D deficiency may be linked to severe asthma: several studies have reported an association between

serum levels of vitamin D and asthma exacerbations.^{79–81} For example, in Puerto Rican children, vitamin D insufficiency is associated with severe asthma exacerbations.⁷⁹ The effect size is greater in non atopic than atopic children suggesting that the role of vitamin D is not related to effects on immune system regulation. Notably, the effect was still observed after controlling for African ancestry and time spent outdoors, suggesting that factors other than UV radiation to the skin were involved. While the children with vitamin D insufficiency were also more obese than those with normal vitamin D levels, it is also possible that dietary differences led to both altered vitamin D intake and to asthma. Interestingly, one report indicates a more substantial effect of central obesity on vitamin D deficiency in women than men⁸² suggesting the possibility that vitamin D deficiency might be linked to sex differences in late onset obese asthma. In contrast to the results of these association studies, Martineau *et al.* found no effect on asthma exacerbations in double-blind randomized placebo-controlled trial of intermittent bolus-dose vitamin D supplementation in adult asthma patients, although the intervention only led to a modest improvement in serum vitamin D levels.⁸³

Systemic inflammation

Obesity results in a state of low grade systemic inflammation. As adipose tissue expands and the distance between adipocytes and capillaries increases, hypoxic death of some adipocytes recruits macrophages into the tissue. Fatty acids released from dead adipocytes cause activation of these macrophages leading to the generation of a variety of inflammatory cytokines, including IL-1 β , TNF α , and IL-6. These cytokines leak into the systemic circulation and may thus impact the lung.⁸⁴ To examine the relationship between systemic inflammation and the severity of asthma, Peters *et al.*⁸⁵ studied two groups of asthmatics: one with severe asthma and one with non-severe asthma. They used serum concentrations of IL-6 as a marker of systemic inflammation. Asthma patients who had IL-6 concentrations higher than the upper 95th percentile value measured in a group of normal health subjects (IL-6 high patients) were more likely to be obese and have hypertension and diabetes than patients with low IL-6 concentrations. Importantly, the IL-6 high patients also had worse lung function and more frequent asthma exacerbations than the IL-6 low patients. It is conceivable that IL-6 itself contributes to worsening of asthma in both the allergic and non-allergic phenotypes of obese asthma. In mice, IL-6 deficiency reduces the eosinophilic airway inflammation and airway hyperresponsiveness induced by allergen sensitization and challenge.⁸⁶ In obese mice, blocking IL-6 signaling with an anti-IL-6 antibody also attenuates the neutrophilic inflammation induced exposure to ozone, a non allergic asthma trigger.⁸⁷ However, it is important to note that many inflammatory mediators are concurrently elevated in patients with systemic inflammation and that IL-6 may simply be a marker of the metabolic dysfunction that creates this inflammation. If so, the observed association between serum IL-6 and asthma severity⁸⁵ may indicate that improving the metabolic dysfunction of obesity may also prove useful for improving the severity of asthma.

IL-1 β is also among the inflammatory mediators that are elevated in the blood of obese individuals.⁸⁸ The release of IL-1 β from cells is dependent upon the activation of caspase-1, which cleaves it from its precursor protein. Caspase-1 is activated upon assembly of the nucleotide oligomerization domain–like receptor protein 3 (NLRP3) inflammasome which can be activated, via toll-like receptor 4 (TLR4) by fatty acids. Increased circulating concentrations of lipids are common in obese subjects⁸⁹ and also increase after a high-fat meal⁹⁰ and increased lung concentrations of fatty acids are also observed in obese mice.⁹¹ Moreover, increased

sputum concentrations of IL-1 β and increased NLRP3 and TLR4 expression in sputum cells are observed in obese versus non obese asthmatic adults.^{90,92} Eating a meal rich in saturated fatty acids also increases NLRP3 and TLR4 expression in sputum cells⁹⁰ and addition of the saturated fatty acid, palmitic acid, to neutrophils and monocytes increases their release of IL-1 β when challenged with lipopolysaccharide or TNF α . Data from mice also indicate a role for the IL-1 β /NLRP3 pathway in obese asthma. Obese mice, including mice rendered obese by high fat diets, exhibit innate airway hyperresponsiveness,⁹³ but this airway hyperresponsiveness is not observed if the obese mice are NLRP3 deficient.⁵²

It is also conceivable that sex differences in the ability of obesity to promote systemic inflammation contribute to the female-predominance of obese asthma. Periyalil *et al.* reported that plasma C-reactive protein (CRP), a marker of systemic inflammation, was higher in obese than non-obese asthmatic adults, but within the obese asthmatic group females had higher CRP than males.⁹⁴ Similar, soluble CD163, a marker of macrophage activation, was higher in obese asthmatic female than male children.⁹⁴

Gut microbiome

Estimates are that more than 100 trillion bacteria from over 1000 different species colonize in human gastrointestinal tract.⁹⁵ Collectively, these bacteria carry at least 100 times more genes than does the entire human genome.^{96,97} There is increasing evidence of a role for the microbiome in obese asthma.^{98,99} Obesity itself alters the community structure of the gut microbiome^{100–104} and eating patterns associated with obesity, including diets with high fat content also affects the gut microbiome.^{105–107} Importantly, other conditions associated with obesity including hyperglycemia, insulin resistance, and systemic inflammation are regulated by the gut microbiome.^{100,108–111} Microbiota also colonize the lung and there are differences in both the gut and lung microbiomes in subjects with asthma.^{112–117} In severe asthmatics, the lung microbiome also differs between obese and non obese subjects.¹¹⁸

There are data linking the gut microbiome to both allergic and non allergic forms of asthma. With respect to allergic asthma, data indicate that early life events that alter the developing gut microbiome (early exposure to antibiotics, formula versus breastfeeding, caesarian versus vaginal delivery, exposure to pets or farm animals) also affect the risk of allergic asthma.¹¹⁹ Several studies have also reported that early life changes in the microbiome are predictive of subsequent asthma development.^{115–117} Data from mice also support a role for the microbiome in asthma. In mouse models of allergic asthma, treatment with certain antibiotics or germ free conditions exacerbate allergic airway responses.^{120–123} Moreover, as in the human studies, the early life window is important for these microbiome-dependent changes: reconstituting germ free mice by fecal transfer from conventional mice attenuates allergic airway responses only when the transfer is performed early in life.¹²²

Our data¹²⁴ indicate that the microbiome also plays a role in the asthma-like phenotype of mice to the non allergic asthma trigger, ozone. However, this role is different from the role of the microbiome in allergic airways disease models. In lean male mice, ozone-induced AHR and ozone-induced neutrophil recruitment to the lungs are reduced following treatment with an antibiotic cocktail (ampicillin, metronidazole, vancomycin, and neomycin). Similar results were obtained in obese female mice in which antibiotics nearly abolish obesity-related increases in ozone-induced AHR.¹²⁵ In lean male mice, a reduction in the magnitude of ozone-induced AHR is also observed in germ free mice versus mice raised under conventional, specific pathogen free conditions, whereas, as described above, allergic airway responses are increased under these conditions.

The mechanistic basis for these effects of the microbiome remains to be established. However, it is increasingly understood that metabolites produced by gut bacteria can accumulate in the circulation and exert effects outside the GI tract, including in the lung. For example, Trompette *et al.*¹²⁶ reported that in mouse models of allergic airways disease, the microbiome acts by generating short chain fatty acids (SCFAs) by via fermentation of dietary fiber. SCFAs enter the blood stream and alter both intestinal and bone marrow immune cells ultimately altering the dendritic cells that are required for allergen-mediated immune responses in the lungs. SCFAs also appear to contribute to the role of the microbiome in ozone-induced AHR in mice, though the role of SCFAs differs in this non allergic model.¹²⁴

It is possible that the microbiome also contributes to the female dominance of late onset obese asthma. There are sex differences in the community structure of the gut microbiome¹²⁷ and our data indicate a role for the microbiome is sex differences in pulmonary response to ozone.¹²⁷ The gut microbiome also regulates sex differences on immune responses.¹²⁸

Collectively, these data suggest that manipulation of the gut microbiome via prebiotics or probiotics might be an important means of regulating the severity of asthma in obese individuals. Regarding prebiotics, in mice, dietary supplementation with inulin, a fermentable fiber that results in SCFA generation, but not cellulose, an insoluble fiber that is not readily fermented, provides protection from the metabolic effects of high fat diets, including glucose tolerance and insulin resistance.¹²⁹ There is some evidence that inulin might also be beneficial in asthmatics. In a small pilot study, Halmes *et al.*¹³⁰ fed stable adult asthmatics a meal containing inulin and probiotics or a control meal. In the group that received inulin but not the control group, there were significant reductions in cell counts and IL-8 in sputum collected 4 h after the meal, as well as a reduction in exhaled nitric oxide, a marker of inflammation. Probiotics may also have beneficial effects against both obesity and asthma. Evidence from mice indicates the ability of probiotics containing Lactobacilli and Bifidobacteria to promote weight loss in animals with diet induced obesity.¹³¹ Data from human studies are much more limited, but a randomized controlled trial of dietary supplementation with a probiotic containing Lactobacillus gasseri for 12 weeks indicated significant effects of the probiotic on weight loss, particularly from the

abdominal region.¹³² Similar effects on weight loss were observed after dietary supplementation with Lactobacillus rhamnosus.¹³³ Treatment with Lactobacillus reduces allergic airway inflammation in mice^{134–136} and there is also evidence that treatment with Lactobacillus gasseri improves lung function and symptoms scores in children with allergic asthma.¹³⁷ Thus, there is reason for optimism that treatment with prebiotics and/or probiotics may prove effective in obese asthmatics, particularly those with severe asthma, but the efficacy of such treatments in this population remains to be established.

Effect of weight loss

Weight loss, whether by diet and exercise or by surgical intervention, improves lung function, asthma control, and asthma-related quality of life (see¹³⁸ for review). For example, Pakhale *et al.*¹³⁹ studied 22 massively obese asthmatics assigned to either a diet or control group for 3 months. The intervention group lost approximately 15% of their body weight and had significant improvements in asthma control, lung function, and asthma quality of life whereas no such changes were observed in the control group. More moderate diet-induced weight loss was also associated with improvements in asthma control in obese asthmatic children.¹⁴⁰ Freitus *et al.*¹⁴¹ performed a study in 55 moderate to severe obese asthmatic adults randomized to dietary restriction with or without exercise. They observed greater weight loss in those assigned to diet plus exercise than those assigned to diet alone. Both groups had improvements in asthma control, but the group assigned to diet plus exercise had greater improvements, and lung function only improved in the diet plus exercise group. Although the extent of weight loss was not as substantial (6.8% and 3.1% in the diet plus exercise versus diet alone groups respectively) as in the study by Pakhale *et al.* described above, but the data suggest an added benefit for exercise over diet alone for obese asthmatics. However, diet alone or diet plus exercise both confer greater improvements than exercise alone.¹⁴² Bariatric surgery, by either sleeve gastrectomy or Roux-en-Y gastric bypass also improves asthma control, asthma-related quality of life, and lung function, and reduces asthma exacerbations.^{36,143,144} In many patients, surgical weight loss also reduced airway hyperresponsiveness,^{36,144} perhaps because obesity alters contractile responses in airway smooth muscle.¹⁴⁵

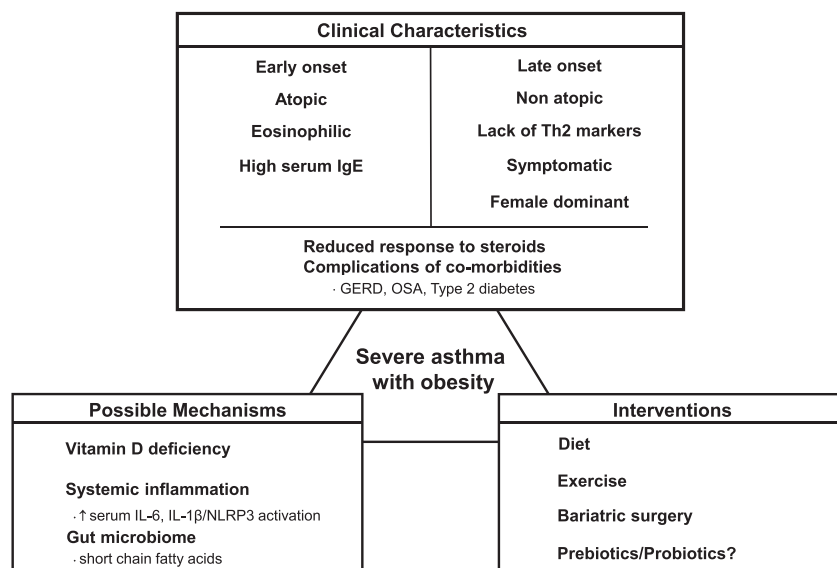


Fig. 1. Proposed features of clinical characteristics, possible mechanisms and interventions for severe asthma with obesity. GERD, Gastroesophageal reflux disease; OSA, obstructive sleep apnea; NLRP3, NLR Family Pyrin Domain Containing 3.

Conclusion

Obesity is very common in severe asthmatics. At least two distinct obese asthma phenotypes have been characterized, one an early onset, allergic phenotype and the other a late onset, female dominated, non allergic phenotype. Importantly, there is also increasing evidence that obesity is causally related to asthma. Better understanding of this relationship may lead to more therapeutic options for this difficult to treat group. For example, weight loss, whether by diet or by surgical intervention has been shown to be efficacious in obese asthmatics. Evidence of a role for the microbiome in obese asthma also suggests that greater attention to components of diet and their impact on the gut microbiome may ultimately prove useful for the obese asthmatic patient (see Fig. 1).

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Conflict of interest

The authors have no conflict of interest to declare.

References

- Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med* 2017;**377**:965–76.
- Sadatsafavi M, Lynd L, Marra C, Carleton B, Tan WC, Sullivan S, et al. Direct health care costs associated with asthma in British Columbia. *Can Respir J* 2010;**17**:74–80.
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;**43**:343–73.
- Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA* 2014;**311**:806–14.
- Skinner AC, Skelton JA. Prevalence and trends in obesity and severe obesity among children in the United States, 1999–2012. *JAMA Pediatr* 2014;**168**:561–6.
- Finkelstein EA, Khavjou OA, Thompson H, Trogon JG, Pan L, Sherry B, et al. Obesity and severe obesity forecasts through 2030. *Am J Prev Med* 2012;**42**:563–70.
- Ministry of Health Labour and Welfare of Japan. *The National Health and Nutrition Survey 2014, 2016*. Available from: https://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyuu_chousa.html (in Japanese).
- Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005;**115**:897–909. quiz 10.
- Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;**175**:661–6.
- Okabe Y, Adachi Y, Itazawa T, Yoshida K, Ohya Y, Odajima H, et al. Association between obesity and asthma in Japanese preschool children. *Pediatr Allergy Immunol* 2012;**23**:550–5.
- Fukutomi Y, Taniguchi M, Nakamura H, Konno S, Nishimura M, Kawagishi Y, et al. Association between body mass index and asthma among Japanese adults: risk within the normal weight range. *Int Arch Allergy Immunol* 2012;**157**:281–7.
- McClean KM, Kee F, Young IS, Elborn JS. Obesity and the lung: 1. *Epidemiol Thorax* 2008;**63**:649–54.
- Lang JE, Hossain J, Dixon AE, Shade D, Wise RA, Peters SP, et al. Does age impact the obese asthma phenotype? Longitudinal asthma control, airway function, and airflow perception among mild persistent asthmatics. *Chest* 2011;**140**:1524–33.
- Camargo Jr CA, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;**159**:2582–8.
- Forno E, Han YY, Libman IM, Muzumdar RH, Cledon JC. Adiposity and asthma in a nationwide study of children and adults in the United States. *Ann Am Thorac Soc* 2018;**15**:322–30.
- Von Behren J, Lipsett M, Horn-Ross PL, Delfino RJ, Gilliland F, McConnell R, et al. Obesity, waist size and prevalence of current asthma in the California Teachers Study cohort. *Thorax* 2009;**64**:889–93.
- Appleton SL, Adams RJ, Wilson DH, Taylor AW, Ruffin RE, North West Adelaide Health Study T. Central obesity is associated with nonatopic but not atopic asthma in a representative population sample. *J Allergy Clin Immunol* 2006;**118**:1284–91.
- Kronander UN, Falkenberg M, Zetterstrom O. Prevalence and incidence of asthma related to waist circumference and BMI in a Swedish community sample. *Respir Med* 2004;**98**:1108–16.
- Brumpton B, Langhammer A, Romundstad P, Chen Y, Mai XM. General and abdominal obesity and incident asthma in adults: the HUNT study. *Eur Respir J* 2013;**41**:323–9.
- Visness CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, et al. Association of childhood obesity with atopic and nonatopic asthma: results from the National Health and Nutrition Examination Survey 1999–2006. *J Asthma* 2010;**47**:822–9.
- Nystad W, Meyer HE, Nafstad P, Tverdal A, Engeland A. Body mass index in relation to adult asthma among 135,000 Norwegian men and women. *Am J Epidemiol* 2004;**160**:969–76.
- Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. *BMC Pediatr* 2013;**13**:121.
- Chen YC, Dong GH, Lin KC, Lee YL. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. *Obes Rev* 2013;**14**:222–31.
- Tsai HJ, Wang G, Hong X, Yao TC, Ji Y, Radovick S, et al. Early life weight gain and development of childhood asthma in a prospective birth cohort. *Ann Am Thorac Soc* 2018;**15**:1197–204.
- Chen Z, Salam MT, Alderete TL, Habre R, Bastain TM, Berhane K, et al. Effects of childhood asthma on the development of obesity among school-aged children. *Am J Respir Crit Care Med* 2017;**195**:1181–8.
- Schatz M, Hsu JW, Zeiger RS, Chen W, Dorenbaum A, Chipps BE, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2014;**133**:1549–56.
- Gibeon D, Batuwita K, Osmond M, Heaney LG, Brightling CE, Niven R, et al. Obesity-associated severe asthma represents a distinct clinical phenotype: analysis of the British Thoracic Society Difficult Asthma Registry Patient cohort according to BMI. *Chest* 2013;**143**:406–14.
- Barros R, Moreira P, Padrao P, Teixeira VH, Carvalho P, Delgado L, et al. Obesity increases the prevalence and the incidence of asthma and worsens asthma severity. *Clin Nutr* 2017;**36**:1068–74.
- Schatz M, Zeiger RS, Zhang F, Chen W, Yang SJ, Camargo Jr CA. Overweight/obesity and risk of seasonal asthma exacerbations. *J Allergy Clin Immunol Pract* 2013;**1**:618–22.
- Hasegawa K, Tsugawa Y, Lopez BL, Smithline HA, Sullivan AF, Camargo Jr CA. Body mass index and risk of hospitalization among adults presenting with asthma exacerbation to the emergency department. *Ann Am Thorac Soc* 2014;**11**:1439–44.
- Luthe SK, Hirayama A, Goto T, Faridi MK, Camargo Jr CA, Hasegawa K. Association between obesity and acute severity among patients hospitalized for asthma exacerbation. *J Allergy Clin Immunol Pract* 2018;**6**:1936–41.
- Rodrigo GJ, Plaza V. Body mass index and response to emergency department treatment in adults with severe asthma exacerbations: a prospective cohort study. *Chest* 2007;**132**:1513–9.
- Okubo Y, Michihata N, Yoshida K, Morisaki N, Matsui H, Fushimi K, et al. Impact of pediatric obesity on acute asthma exacerbation in Japan. *Pediatr Allergy Immunol* 2017;**28**:763–7.
- Haldrup P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;**178**:218–24.
- Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;**181**:315–23.
- Dixon AE, Pratley RE, Forgione PM, Kaminsky DA, Whittaker-Leclair LA, Griffes LA, et al. Effects of obesity and bariatric surgery on airway hyper-responsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011;**128**:508–15. e1–2.
- Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, et al. Cluster analysis of obesity and asthma phenotypes. *PLoS One* 2012;**7**:e36631.
- Carr TF, Kraft M. Use of Biomarkers to identify phenotypes and endotypes of severe asthma. *Ann Allergy Asthma Immunol* 2018;**121**:414–20.
- Pradeepan S, Garrison G, Dixon AE. Obesity in asthma: approaches to treatment. *Curr Allergy Asthma Rep* 2013;**13**:434–42.
- Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med* 2007;**101**:2240–7.
- 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**:682–7.
- Peters MC, Kerr S, Dunican EM, Woodruff PG, Fajt ML, Levy BD, et al. Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* 2018. <https://doi.org/10.1016/j.jaci.2017.12.1009>.
- Maltby S, Tay HL, Yang M, Foster PS. Mouse models of severe asthma: understanding the mechanisms of steroid resistance, tissue remodelling and disease exacerbation. *Respirology* 2017;**22**:874–85.
- Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012;**18**:716–25.
- Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, et al. Obesity and asthma: an association modified by age of asthma onset. *J Allergy Clin Immunol* 2011;**127**:1486–93. e2.
- Bruijnzeel PL, Uddin M, Koenderman L. Targeting neutrophilic inflammation in severe neutrophilic asthma: can we target the disease-relevant neutrophil phenotype? *J Leukoc Biol* 2015;**98**:549–56.

47. Panettieri Jr RA. Neutrophilic and pauci-immune phenotypes in severe asthma. *Immunol Allergy Clin North Am* 2016;**36**:569–79.
48. Scott HA, Gibson PG, Garg ML, Wood LG. Airway inflammation is augmented by obesity and fatty acids in asthma. *Eur Respir J* 2011;**38**:594–602.
49. Marijse GS, Seys SF, Schelpe AS, Dilissen E, Goeminne P, Dupont LJ, 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**:1284–5.
50. Chen JH, Qin L, Shi YY, Feng JT, Zheng YL, Wan YF, 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;**121**:48–58.
51. Tashiro H, Takahashi K, Sadamatsu H, Kato G, Kurata K, Kimura S, et al. Saturated fatty acid increases lung macrophages and augments house dust mite-induced airway inflammation in mice fed with high-fat diet. *Inflammation* 2017;**40**:1072–86.
52. Kim HY, Lee HJ, Chang YJ, Pichavant M, Shore SA, Fitzgerald KA, et al. Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. *Nat Med* 2014;**20**:54–61.
53. Mathews JA, Krishnamoorthy N, Kasahara DI, Hutchinson J, Cho Y, Brand JD, et al. Augmented responses to ozone in obese mice require IL-17A and gastrin-releasing peptide. *Am J Respir Cell Mol Biol* 2018;**58**:341–51.
54. Desai D, Newby C, Symon FA, Haldar P, Shah S, Gupta S, et al. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. *Am J Respir Crit Care Med* 2013;**188**:657–63.
55. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J* 2015;**46**:1308–21.
56. Maio S, Baldacci S, Bresciani M, Simoni M, Latorre M, Murgia N, et al. RItA: the Italian severe/uncontrolled asthma registry. *Allergy* 2018;**73**:683–95.
57. Andersen LI, Schmidt A, Bundgaard A. Pulmonary function and acid application in the esophagus. *Chest* 1986;**90**:358–63.
58. Hanauer SB. Update on the etiology, pathogenesis and diagnosis of ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol* 2004;**1**:26–31.
59. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med* 2017;**195**:302–13.
60. Rogers L. Role of sleep apnea and gastroesophageal reflux in severe asthma. *Immunol Allergy Clin North Am* 2016;**36**:461–71.
61. Davies SE, Bishopp A, Wharton S, Turner AM, Mansur AH. The association between asthma and obstructive sleep apnea (OSA): a systematic review. *J Asthma* 2018:1–12.
62. Julien JY, Martin JG, Ernst P, Olivenstein R, Hamid Q, Lemiere C, et al. Prevalence of obstructive sleep apnea-hypopnea in severe versus moderate asthma. *J Allergy Clin Immunol* 2009;**124**:371–6.
63. Wang Y, Liu K, Hu K, Yang J, Li Z, Nie M, et al. Impact of obstructive sleep apnea on severe asthma exacerbations. *Sleep Med* 2016;**26**:1–5.
64. Teodorescu M, Brodyman O, Curran-Everett D, Sorkness RL, Crisafi G, Blecker ER, et al. Obstructive sleep apnea risk, asthma burden, and lower airway inflammation in adults in the Severe Asthma Research Program (SARP) II. *J Allergy Clin Immunol Pract* 2015;**3**:566–75. e1.
65. Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation* 2003;**107**:1129–34.
66. Karamanli H, Ozol D, Ugru KS, Yildirim Z, Armutcu F, Bozkurt B, et al. Influence of CPAP treatment on airway and systemic inflammation in OSAS patients. *Sleep Breath* 2014;**18**:251–6.
67. Simard B, Turcotte H, Marceau P, Biron S, Hould FS, Lebel S, et al. Asthma and sleep apnea in patients with morbid obesity: outcome after bariatric surgery. *Obes Surg* 2004;**14**:1381–8.
68. Cardet JC, Ash S, Kusa T, Camargo Jr CA, Israel E. Insulin resistance modifies the association between obesity and current asthma in adults. *Eur Respir J* 2016;**48**:403–10.
69. Forno E, Han YY, Muzumdar RH, Celedon JC. Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma. *J Allergy Clin Immunol* 2015;**136**:304–11. e8.
70. Rastogi D, Bhalani K, Hall CB, Isasi CR. Association of pulmonary function with adiposity and metabolic abnormalities in urban minority adolescents. *Ann Am Thorac Soc* 2014;**11**:744–52.
71. Rastogi D, Fraser S, Oh J, Huber AM, Schulman Y, Bhagatani RH, et al. Inflammation, metabolic dysregulation, and pulmonary function among obese urban adolescents with asthma. *Am J Respir Crit Care Med* 2015;**191**:149–60.
72. Singh S, Bodas M, Bhatraju NK, Pattanaik B, Gheware A, Parameswaran PK, et al. Hyperinsulinemia adversely affects lung structure and function. *Am J Physiol Lung Cell Mol Physiol* 2016;**310**:L837–45.
73. Li CY, Erickson SR, Wu CH. Metformin use and asthma outcomes among patients with concurrent asthma and diabetes. *Respirology* 2016;**21**:1210–8.
74. Dixon AE, Subramanian M, DeSarno M, Black K, Lane L, Holguin F. A pilot randomized controlled trial of pioglitazone for the treatment of poorly controlled asthma in obesity. *Respir Res* 2015;**16**:143.
75. Afzal S, Brondum-Jacobsen P, Bojesen SE, Nordestgaard BG. Vitamin D concentration, obesity, and risk of diabetes: a mendelian randomisation study. *Lancet Diabetes Endocrinol* 2014;**2**:298–306.
76. Vimalaswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med* 2013;**10**:e1001383.
77. Wortsman J, Matsuo LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000;**72**:690–3.
78. 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**:341–9.
79. Szentpetery SE, Han YY, Brehm JM, Acosta-Perez E, Forno E, Boutaoui N, et al. Vitamin D insufficiency, plasma cytokines, and severe asthma exacerbations in school-aged children. *J Allergy Clin Immunol Pract* 2018;**6**:289–91. e2.
80. Brehm JM, Schuermann B, Fuhlbrigge AL, Hollis BW, Strunk RC, Zeiger RS, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol* 2010;**126**:52–8. e5.
81. Brehm JM, Celedon JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 2009;**179**:765–71.
82. Karonova T, Belyaeva O, Jude EB, Tsiberkin A, Andreeva A, Grineva E, et al. Serum 25(OH)D and adipokines levels in people with abdominal obesity. *J Steroid Biochem Mol Biol* 2018;**175**:170–6.
83. Martineau AR, MacLaughlin BD, Hooper RL, Barnes NC, Jolliffe DA, Greiller CL, et al. Double-blind randomised placebo-controlled trial of bolus-dose vitamin D3 supplementation in adults with asthma (ViDiAs). *Thorax* 2015;**70**:451–7.
84. McNelis JC, Olefsky JM. Macrophages, immunity, and metabolic disease. *Immunity* 2014;**41**:36–48.
85. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respir Med* 2016;**4**:574–84.
86. Lin YL, Chen SH, Wang JY. Critical role of IL-6 in dendritic cell-induced allergic inflammation of asthma. *J Mol Med (Berl)* 2016;**94**:51–9.
87. Lang JE, Williams ES, Mizgerd JP, Shore SA. Effect of obesity on pulmonary inflammation induced by acute ozone exposure: role of interleukin-6. *Am J Physiol Lung Cell Mol Physiol* 2008;**294**:L1013–20.
88. Parisi MM, Grun LK, Lavandoski P, Alves LB, Bristot JJ, Mattiello R, et al. Immunosenescence induced by plasma from individuals with obesity caused cell signaling dysfunction and inflammation. *Obesity* 2017;**25**:1523–31.
89. Miller WM, Nori-Janosz KE, Lillystone M, Yanez J, McCullough PA. Obesity and lipids. *Curr Cardiol Rep* 2005;**7**:465–70.
90. Wood LG, Li Q, Scott HA, Rutting S, Berthon BS, Gibson PG, et al. Saturated fatty acids, obesity, and the nucleotide oligomerization domain-like receptor protein 3 (NLRP3) inflammasome in asthmatic patients. *J Allergy Clin Immunol* 2018. <https://doi.org/10.1016/j.jaci.2018.04.037>.
91. Mathews JA, Kasahara DI, Cho Y, Bell LN, Gunst PR, Karoly ED, et al. Effect of acute ozone exposure on the lung metabolomes of obese and lean mice. *PLoS One* 2017;**12**:e0181017.
92. 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**:1133–40.
93. Shore SA. Mechanistic basis for obesity-related increases in ozone-induced airway hyperresponsiveness in mice. *Ann Am Thorac Soc* 2017;**14**(Suppl 5):S357–62.
94. Periyalil HA, Wood LG, Scott HA, Jensen ME, Gibson PG. Macrophage activation, age and sex effects of immunometabolism in obese asthma. *Eur Respir J* 2015;**45**:388–95.
95. Ley RE, Peterson DA, Gordon JL. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell* 2006;**124**:837–48.
96. Hamady M, Knight R. Microbial community profiling for human microbiome projects: tools, techniques, and challenges. *Genome Res* 2009;**19**:1141–52.
97. Ursell LK, Haiser HJ, Van Treuren W, Garg N, Reddivari L, Vanamala J, et al. The intestinal metabolome: an intersection between microbiota and host. *Gastroenterology* 2014;**146**:1470–6.
98. Cho Y, Shore SA. Obesity, asthma, and the microbiome. *Physiology* 2016;**31**:108–16.
99. Shore SA, Cho Y. Obesity and asthma: microbiome-metabolome interactions. *Am J Respir Cell Mol Biol* 2016;**54**:609–17.
100. Ley RE. Obesity and the human microbiome. *Curr Opin Gastroenterol* 2010;**26**:5–11.
101. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JL. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A* 2005;**102**:11070–5.
102. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, et al. A core gut microbiome in obese and lean twins. *Nature* 2009;**457**:480–4.
103. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JL. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006;**444**:1027–31.
104. Rosenbaum M, Knight R, Leibel RL. The gut microbiota in human energy homeostasis and obesity. *Trends Endocrinol Metab* 2015;**26**:493–501.
105. de Wit N, Derrien M, Bosch-Vermeulen H, Oosterink E, Keshtkar S, Duval C, et al. Saturated fat stimulates obesity and hepatic steatosis and affects gut microbiota composition by an enhanced overflow of dietary fat to the distal intestine. *Am J Physiol Gastrointest Liver Physiol* 2012;**303**:G589–99.
106. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JL. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci Transl Med* 2009;**1**:6ra14.
107. Zhang C, Zhang M, Wang S, Han R, Cao Y, Hua W, et al. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. *ISME J* 2010;**4**:232–41.

108. Cani PD, Delzenne NM, Amar J, Burcelin R. Role of gut microflora in the development of obesity and insulin resistance following high-fat diet feeding. *Pathol Biol (Paris)* 2008;**56**:305–9.
109. Kimura I, Ozawa K, Inoue D, Imamura T, Kimura K, Maeda T, et al. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. *Nat Commun* 2013;**4**:1829.
110. Karlsson FH, Tremaroli V, Nookaew I, Bergstrom G, Behre CJ, Fagerberg B, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* 2013;**498**:99–103.
111. Nagpal R, Kumar M, Yadav AK, Hemalatha R, Yadav H, Marotta F, et al. Gut microbiota in health and disease: an overview focused on metabolic inflammation. *Benef Microbes* 2016;**7**:181–94.
112. Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, et al. Disordered microbial communities in asthmatic airways. *PLoS One* 2010;**5**:e8578.
113. Huang YJ, Nelson CE, Brodie EL, Desantis TZ, Baek MS, Liu J, et al. Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. *J Allergy Clin Immunol* 2011;**127**:372–81. e1–3.
114. van Nimwegen FA, Penders J, Stobberingh EE, Postma DS, Koppelman GH, Kerkhof M, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *J Allergy Clin Immunol* 2011;**128**:948–55. e1–3.
115. Arrieta MC, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* 2015;**7**:307ra152.
116. Stokholm J, Blaser MJ, Thorsen J, Rasmussen MA, Waage J, Vinding RK, et al. Maturation of the gut microbiome and risk of asthma in childhood. *Nat Commun* 2018;**9**:141.
117. Durack J, Kimes NE, Lin DL, Rauch M, McKean M, McCauley K, et al. Delayed gut microbiota development in high-risk for asthma infants is temporally modifiable by *Lactobacillus* supplementation. *Nat Commun* 2018;**9**:707.
118. Huang YJ, Nariya S, Harris JM, Lynch SV, Choy DF, Arron JR, et al. The airway microbiome in patients with severe asthma: Associations with disease features and severity. *J Allergy Clin Immunol* 2015;**136**:874–84.
119. Arrieta MC, Finlay B. The intestinal microbiota and allergic asthma. *J Infect* 2014;**69**(Suppl 1):S53–5.
120. Herbst T, Sichelstiel A, Schar C, Yadava K, Burki K, Cahenzli J, et al. Dysregulation of allergic airway inflammation in the absence of microbial colonization. *Am J Respir Crit Care Med* 2011;**184**:198–205.
121. Arnold IC, Dehzad N, Reuter S, Martin H, Becher B, Taube C, et al. *Helicobacter pylori* infection prevents allergic asthma in mouse models through the induction of regulatory T cells. *J Clin Invest* 2011;**121**:3088–93.
122. Olszak T, An D, Zeissig S, Vera MP, Richter J, Franke A, et al. Microbial exposure during early life has persistent effects on natural killer T cell function. *Science* 2012;**336**:489–93.
123. Russell SL, Gold MJ, Hartmann M, Willing BP, Thorson L, Wlodarska M, et al. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep* 2012;**13**:440–7.
124. Cho Y, Abu-Ali G, Tashiro H, Kasahara DI, Brown TA, Brand JD, et al. The microbiome regulates pulmonary responses to ozone in mice. *Am J Respir Cell Mol Biol* 2018;**59**:346–54.
125. Cho Y, Kasahara DI, Abu-Ali G, Huttenhower C, Shore SA. Role of the gut microbiome in obesity-related increases in pulmonary responses to ozone: sex differences. *Am J Respir Crit Care Med* 2016;**193**:A1077.
126. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med* 2014;**20**:159–66.
127. Cho Y, Abu-Ali G, Tashiro H, Brown TA, Osgood R, Kasahara DI, et al. Sex differences in pulmonary responses to ozone in mice: role of the microbiome. *Am J Respir Cell Mol Biol* 2018. <https://doi.org/10.1165/rcmb.2018-0099OC>.
128. Elderman M, de Vos P, Faas M. Role of microbiota in sexually dimorphic immunity. *Front Immunol* 2018;**9**:1018.
129. Zou J, Chassaing B, Singh V, Pellizzon M, Ricci M, Fythe MD, et al. Fiber-mediated nourishment of gut microbiota protects against diet-induced obesity by restoring IL-22-mediated colonic health. *Cell Host Microbe* 2018;**23**:41–53. e4.
130. Haines I, Baines KJ, Berthon BS, MacDonald-Wicks LK, Gibson PG, Wood LG. Soluble fibre meal challenge reduces airway inflammation and expression of GPR43 and GPR41 in asthma. *Nutrients* 2017;**9**. <https://doi.org/10.3390/nu9010057>.
131. Nova E, Perez de Heredia F, Gomez-Martinez S, Marcos A. The role of probiotics on the microbiota: effect on obesity. *Nutr Clin Pract* 2016;**31**:387–400.
132. Kadooka Y, Sato M, Ogawa A, Miyoshi M, Uenishi H, Ogawa H, et al. Effect of *Lactobacillus gasseri* SBT2055 in fermented milk on abdominal adiposity in adults in a randomised controlled trial. *Br J Nutr* 2013;**110**:1696–703.
133. Sanchez M, Darimont C, Drapeau V, Emady-Azar S, Lepage M, Rezzonico E, et al. Effect of *Lactobacillus rhamnosus* CGMCC1.3724 supplementation on weight loss and maintenance in obese men and women. *Br J Nutr* 2014;**111**:1507–19.
134. Forsythe P, Inman MD, Bienenstock J. Oral treatment with live *Lactobacillus reuteri* inhibits the allergic airway response in mice. *Am J Respir Crit Care Med* 2007;**175**:561–9.
135. Jan RL, Yeh KC, Hsieh MH, Lin YL, Kao HF, Li PH, et al. *Lactobacillus gasseri* suppresses Th17 pro-inflammatory response and attenuates allergen-induced airway inflammation in a mouse model of allergic asthma. *Br J Nutr* 2012;**108**:130–9.
136. Kim HJ, Kim YJ, Lee SH, Yu J, Jeong SK, Hong SJ. Effects of *Lactobacillus rhamnosus* on allergic march model by suppressing Th2, Th17, and TSLP responses via CD4(+)CD25(+)Foxp3(+) Tregs. *Clin Immunol* 2014;**153**:178–86.
137. Chen YS, Jan RL, Lin YL, Chen HH, Wang JY. Randomized placebo-controlled trial of *Lactobacillus* on asthmatic children with allergic rhinitis. *Pediatr Pulmonol* 2010;**45**:1111–20.
138. Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol* 2018;**141**:1169–79.
139. 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**:1582–90.
140. Jensen ME, Gibson PG, Collins CE, Hilton JM, Wood LG. Diet-induced weight loss in obese children with asthma: a randomized controlled trial. *Clin Exp Allergy* 2013;**43**:775–84.
141. Freitas PD, Ferreira PG, Silva AG, Stelmach R, Carvalho-Pinto RM, Fernandes FL, et al. The role of exercise in a weight-loss program on clinical control in obese adults with asthma. A randomized controlled trial. *Am J Respir Crit Care Med* 2017;**195**:32–42.
142. Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, et al. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. *Clin Exp Allergy* 2013;**43**:36–49.
143. Hasegawa K, Tsugawa Y, Chang Y, Camargo Jr CA. Risk of an asthma exacerbation after bariatric surgery in adults. *J Allergy Clin Immunol* 2015;**136**:288–94. e8.
144. Boulet LP, Turcotte H, Martin J, Poirier P. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respir Med* 2012;**106**:651–60.
145. Orfanos S, Jude J, Deeney BT, Cao G, Rastogi D, van Zee M, et al. Obesity increases airway smooth muscle responses to contractile agonists. *Am J Physiol Lung Cell Mol Physiol* 2018. <https://doi.org/10.1152/ajplung.00459.2017>.