

Role of Weight Management in Asthma Symptoms and Control



Timothy Heacock, MD, Njira Lugogo, MD*

KEYWORDS

• Obesity • Asthma • Weight loss • Gastric bypass surgery • Asthma control

KEY POINTS

- Weight loss achieved by both dietary and surgical interventions improves asthma symptoms and control.
- There may be a subset of obese patients with asthma who receive added benefits from weight loss. These patients tend to have late-onset asthma that is preceded by obesity and have decreased airway hyperresponsiveness with weight loss.
- More research is needed to determine whether the physiologic changes that occur with obesity are responsible for the improvements in asthma symptoms.
- Weight loss should be recommended to patients with poor asthma control; however, there are insufficient data to support surgical interventions for weight loss solely for the purpose of improving asthma control.

INTRODUCTION

The prevalence of obesity has increased significantly over the past several decades, with more than a third of adults in the United States now considered obese (body mass index [BMI] >30) according to a recent report from the US Centers for Disease Control and Prevention. Obesity has a known association with diabetes mellitus type 2, hypertension, and atherosclerotic heart disease. Over the past decade it has become increasingly recognized that obesity is associated with asthma, with an increased risk of developing asthma with increasing BMI in a dose-response manner.¹ In addition, overweight/obese patients with asthma have more symptoms, poor asthma control, and decreased response to conventional asthma therapies, including inhaled steroids.² Patients who are morbidly obese bear the greatest morbidity from asthma and the prevalence of asthma in the bariatric surgery population is as high

Conflicts of interest: Drs T. Heacock and N. Lugogo have no conflicts of interest related to the topic of this article.

Department of Pulmonary and Critical Care, Duke University Medical Center, Durham, NC 27710, USA

* Corresponding author.

E-mail address: njira.lugogo@duke.edu

Immunol Allergy Clin N Am 34 (2014) 797–808

<http://dx.doi.org/10.1016/j.iac.2014.07.009>

immunology.theclinics.com

0889-8561/14/\$ – see front matter © 2014 Elsevier Inc. All rights reserved.

as 10%.³ Obesity has also been recognized as a risk factor for more severe and difficult-to-treat asthma, and obese patients with asthma have poor response to conventional asthma therapies including inhaled steroids, which is thought to be caused by glucocorticoid resistance.^{2,4,5} Animal models and epidemiologic studies have suggested that leptin, a hormone that regulates satiety and is increased in obesity, and adiponectin, an antiinflammatory hormone that is present in decreased levels in obesity, may play a role in allergic airway inflammation and subsequently cause worsening asthma.^{6,7} Proposed mechanisms for the increased risk of asthma in obesity include shallow tidal breathing caused by decreased chest wall compliance causing decreased airway smooth muscle stretch and increased hyperresponsiveness, increased incidence of gastroesophageal reflux, sleep-disordered breathing (SDB), misdiagnosis of asthma, genetic polymorphism, and effects of systemic cytokines associated with obesity on inflammation in the lungs.^{8–11} There is likely a causal relationship between obesity and asthma and thus targeting weight loss in individuals who are overweight/obese with asthma is likely to lead to improved asthma control and may even cause reversal of inflammation and potentially fully resolve asthma in patients for whom obesity is the primary cause of disease.

This article discusses the effect of weight loss via dietary modifications and surgical interventions on asthma symptoms and control. It is concerned with the effect of weight loss on inflammatory mediators of asthma and the impact of alterations in inflammation on asthma.

DIETARY INTERVENTIONS IN WEIGHT MANAGEMENT

There are several observational studies that have been performed to determine the effect of changes in weight on asthma control and symptoms ([Table 1](#)). A study from the United Kingdom followed 151 patients with severe asthma (75% with BMI > 25 and 44% with BMI > 30) over a 1-year period and monitored changes in their weight. There was no correlation with changes in weight and asthma exacerbations or Asthma Control Questionnaire (ACQ) scores. However, there was a correlation between weight change and forced expiratory volume in 1 second (FEV₁) with increased FEV₁ associated with decreases in weight ($r = -0.3$; $P = .03$).¹² In a larger cohort of patients, Haselkorn and colleagues¹³ evaluated patients from The Epidemiology and Natural history of Asthma: Outcomes and Treatment Regimens (TENOR) study with severe or difficult-to-treat asthma divided into 3 groups based on changes in weight over a 1-year period. The groups were divided into those patients that had greater than or equal to 2.3-kg (5-lb) weight loss, less than 2.3-kg change in weight, or greater than or equal to 2.3-kg weight gain. Those who gained weight reported poor asthma control and required a greater number of steroid bursts for asthma exacerbations. The patients who lost weight did not experience improvements in asthma control. However, this study is limited by the inclusion of nonobese individuals and the low threshold of weight loss that is likely to result in low power to detect a difference in asthma control associated with weight loss.

These observational studies indicated that obesity is associated with poorer asthma control, quality of life, and increased exposure to oral steroids. In these initial studies the effect of weight loss on lung function measures was unclear because there were contrary findings with regard to FEV₁. Based on these findings, several investigators designed studies that incorporated weight loss interventions to determine the effect of weight loss on markers of asthma control, quality of life, and lung function measures.

Stenius-Aarniala and colleagues¹⁴ completed an unblinded randomized controlled trial of 38 obese patients with asthma assessing the effects of a 14-week weight

reduction program using a low-calorie diet (1757 kJ [420 cal]) versus no intervention. The subjects in the intervention group lost 14.5% of their pretreatment weight and this weight loss was sustained at 11.3% after 1 year. In comparison, the controls lost 0.3% during the study and gained 2.2% of their pretreatment weight at 1 year. The intervention group showed improvements in FEV₁, forced vital capacity (FVC), use of rescue medication, and number of exacerbations at the conclusion of the study. The improvements in FEV₁ and FVC persisted at the 1-year follow-up visit; however, the improvement in rescue medication use was no longer significant. Although there was no improvement in health status based on the St George's Respiratory Questionnaire at the conclusion of the study, there were significant differences in scores at 6 months and a year. This study was the first to show that a nonsurgical weight loss intervention could lead to sustained improvement in lung function and health status. In a follow-up study by the same investigators, 14 subjects had significant improvements in peak expiratory flow (PEF) diurnal variation, day-to-day PEF variation, and airway resistance with similar improvements in FEV₁ and FVC.¹⁵ Based on these findings, the investigators suggested that weight loss may improve asthma through changes in lung mechanics and decreased airway obstruction.

Johnson and colleagues¹⁶ noted improvements in self-reported symptoms and PEF rate but not FEV₁ with an alternating-day low-calorie diet that resulted in an average of 8.5% loss of pretreatment weight. The improvements in lung function occurred within 2 weeks of initiating the diet, suggesting that changes in inflammatory mediators and other effects of changes in diet may have caused improvements in lung function even in the absence of significant weight loss. Other studies have noted similar improvements in need for rescue bronchodilator use associated with dietary modifications exclusive of weight loss. Hernandez Romero¹⁷ showed that subjects treated with a premixed protein powder diet did not require albuterol during the study, compared with 90% of patients requiring albuterol for rescue in the group receiving a personalized meal plan. The difference in rescue medication use may be explained partially by the difference in the dietary interventions (ie, components of the two diets) or a greater decrease in BMI.

If asthma is a consequence of systemic changes associated with diet and not obesity alone, then dietary changes may mitigate inflammation via alteration of systemic cytokines or changes in the microbiome with downstream alteration of immune responses. This alteration would be a plausible explanation for why asthma symptoms improve before the presence of weight loss or to a greater extent in the context of specific dietary formulations.

Weight loss has positive effects on lung function in subjects with and without asthma. A study of 58 women (24 with asthma, 34 without asthma) enrolled in an intensive 6-month weight loss regimen recorded an average decrease in weight of 20 kg. The FEV₁ and FVC increased significantly (92 mL and 73 mL respectively) for every 10% loss in body weight.¹⁸ Bronchial hyperresponsiveness as measured by response to methacholine was not altered by weight loss, a finding that was reproduced in a study that focused on overweight/obese subjects with asthma.^{18,19} However, the conclusions that can be drawn are limited by the sample size and the inclusion of patients without asthma in one of the studies, because this may confound the results.

The role of exercise as an intervention has not been studied extensively. A study that examined the effect of weight loss induced by diet, exercise, or a combination of diet and exercise on asthma symptoms and quality of life noted that exercise alone was insufficient in improving asthma control as measured by the ACQ. Asthma control improved after the dietary and combined interventions with a significant decrease in ACQ scores

Table 1
Changes in markers of asthma control and lung function following dietary weight loss interventions

Study	Design	Population	Intervention	Measured	Changes
Stenius-Aarniala et al, ¹⁴ 2000	Randomized controlled trial	Obese asthmatics	14-wk weight reduction program with 8-wk low-calorie diet	Spirometry, PEF Self-reported medication use and exacerbation SQRQ	Improvement in FEV ₁ , FVC, use of rescue medication, and number of exacerbations Sustained improvement in SGRQ
Hakala et al, ¹⁵ 2000	Observational	14 obese asthmatics	14 wk weight reduction program with 8-wk low-calorie diet	PEF Spirometry Lung volumes Minute ventilation	Improvement in spirometry, lung volumes, and minute ventilation Decrease in variability of PEF
Aaron et al, ¹⁸ 2004	Observation	58 obese women, 24 with asthma	6-mo weight loss program	Spirometry Lung volume Methacholine challenge	Improvement in FEV ₁ , FVC in those who lost weight No change in airway responsiveness
Johnson et al, ¹⁶ 2007	Prospective cohort	10 obese moderate persistent asthma	8-wk, alternating-day low-calorie diet	ACQ, mini-AQLQ, ASUI Spirometry PEF	Improvement in all questionnaires and PEF No change in spirometry

Haselkorn et al, ¹³ 2009	Observational	2396 difficult-to-treat asthmatics	3 groups at 1 y, (lost, maintained, or gained weight)	ATAQ AQLQ Number of steroid bursts	Patients who gained weight had worse questionnaire scores and more steroid bursts Patients who lost weight noted no change
Bafadhel et al, ¹² 2010	Observational	151 asthmatics	3 groups at 1 y, (lost, maintained, or gained weight)	Spirometry ACQ	No change in ACQ with weight loss Change in FEV ₁ correlates with weight change
Scott et al, ²⁰ 2013	Randomized control trial	46 obese asthmatics	10 wk, diet, exercise, or combination	AQLQ ACQ	AQLQ improved in all groups ACQ only changed in the diet and combination groups
Dias-Junior et al, ¹⁹ 2013	Randomized trial	33 moderately obese asthmatics with severe asthma	22 diet and pharmacologic weight loss, 11 control followed at 6 mo	ACQ Rescue medication use Methacholine challenge Spirometry	Improvement in ACQ, FVC, and rescue medication use in weight loss group No change in methacholine challenge response

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ASUI, Asthma Symptom Utility Index; ATAQ, Asthma Therapy Assessment Questionnaire; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; SGRQ, St. George Respiratory Questionnaire.

(mean $\pm$ standard deviation, -0.6 ± 0.5 , $P = .001$ and -0.5 ± 0.7 ; $P = .040$). The ability of reductions in weight to improve asthma control as measured by the ACQ score was further shown in a study by Dias-Junior and colleagues.¹⁹ Weight loss and changes in waist circumference and fat mass were significantly greater for the dietary and combined interventions compared with exercise alone and quality of life based on Asthma Quality of Life Questionnaire (AQLQ) scores improved in all groups. The investigators therefore concluded that even a modest amount of weight loss equal to 5% to 10% of total body weight is associated with clinically important improvements in asthma control as defined by a decrease in ACQ score of greater than or equal to 0.5 and in quality of life defined as a change in AQLQ score of greater than or equal to 0.5.²⁰ These findings are clinically meaningful and suggest that weight loss should be included in the armamentarium of clinical interventions used to manage patients with asthma who are also obese.

SURGICAL INTERVENTION FOR WEIGHT LOSS

Calorie restriction and behavioral modification may be difficult and ineffective in achieving and sustaining a significant amount of weight loss in most morbidly obese patients. Given the increased interest in and prevalence of bariatric surgery as a preferred therapy for morbidly obese adults, we sought to determine whether weight lost via surgical interventions resulted in greater alterations in asthma control and airway hyperresponsiveness (AHR). Early observational studies of bariatric surgery all showed significant improvements in asthma control.^{21–26} One of the earliest studies, by Macgregor and Greenberg²¹ followed 40 morbidly obese patients with asthma for an average of 4 years (2–11 years) after bariatric surgery. There was an improvement in symptoms or decreased medication use in 90% of patients and 48% of patients reported complete resolution of their asthma.²¹ Furthermore, 5 of the 40 patients experienced increased asthma symptoms on regaining weight and all these symptoms resolved with revision of bariatric surgery. A similar study by Dixon and colleagues²² followed 32 consecutive patients with a physician diagnosis of asthma for a year and administered standard asthma questionnaires after bariatric surgery. During the 1-year follow-up significant decreases in BMI were noted from an average of 45.7 kg/m² before surgery to 32.9 kg/m² after surgery. The patients were noted concurrently to have an improvement in all asthma-related symptoms assessed by questionnaire, including decreased severity and impact on daily activities, asthma medication use, asthma-related hospitalizations, sleep interruption, and impairments in exercise capacity. Additional observational studies have shown similar improvements in asthma control with complete resolution of asthma symptoms and discontinuation of asthma medicines in 48% to 80% of subjects after bariatric surgery depending on the study.^{23–27}

Additional studies have been designed to determine the effect of bariatric surgery on asthma by studying respiratory prescription drug claims.²⁸ A large cross-sectional study of subjects with asthma in the Swedish Obese Subjects intervention study showed a decrease in asthma-related drug costs in the surgically treated patients, whereas there was an increased cost among patients treated conventionally.²⁶ A similar study in the United States that followed a cohort of 320 patients for 1 year before and after bariatric surgery also revealed a decrease in the number of prescriptions for asthma-related medications in the first postsurgical year. Only 43% of patients who filled a prescription in the year before surgery filled prescriptions in the year after surgery. Similar results were found when these analyses were restricted to patients with a physician's diagnosis of asthma.²⁹

Although these observational studies are intriguing, they largely relied on patient-reported symptoms or medication use as markers of asthma improvement. More recent studies have included objective measures of pulmonary function, AHR, and inflammation. One of the first was a small prospective trial by Maniscalco and colleagues³⁰ in which 12 obese female subjects with asthma underwent laparoscopic adjustable gastric banding (LAGB) and 10 who did not undergo surgery were followed for 1 year. The intervention group had a significantly improved Asthma Control Test score, FEV₁, and FVC, whereas the control group showed no significant change. The control group had no change in BMI, in contrast with the intervention group whose mean BMI was 45.2 ± 4.7 before surgery, which decreased to 34.8 ± 4.2 after surgery.

Boulet and colleagues³¹ completed a study that included 12 patients with asthma undergoing bariatric surgery and 11 not undergoing surgery and noted improvements in ACQ scores and pulmonary function testing. This study also showed that AHR as defined by methacholine challenge (PC20) testing improved after bariatric surgery and that improvement in PC20 was significantly correlated with the change in BMI and C-reactive peptide levels.³² The change in AHR occurred independently of presence/absence of atopy and metabolic syndrome. Dixon and colleagues³² followed 23 subjects with asthma for 12 months after bariatric surgery. Bariatric surgery resulted in similar improvements in ACQ scores and FEV₁. There were no significant changes in AHR in the group overall. A post-hoc analysis of surgical subjects divided into 2 groups based on immunoglobulin E (IgE) greater than or less than 100 IU/mL was performed and showed significant improvement in AHR in subjects with IgE levels less than 100 IU/mL but not in those with high IgE levels. These findings suggest that type 2 helper T cell response (TH2) status at baseline may affect response to bariatric surgery. Although patients with TH2 high status had improvements in asthma control and FEV₁ they did not have any changes in AHR. This finding indicates that the TH2 low phenotype may have AHR that is mediated directly by obesity-related mechanisms such as increased cholinergic tone or increased neurogenic inflammation that improves with weight loss and results in decreases in AHR.

We were interested in determining whether the effects on asthma associated with bariatric surgery vary based on surgical technique. A study of 257 patients with asthma who completed a 1-year follow-up survey after bariatric surgery showed an overall reduction in asthma medication use in all patients; however, those who underwent LAGB were only 37% as likely to show improvement in self-reported asthma severity as those with the Roux-en-Y procedure. This finding may be related to the lower percentage of weight loss associated with this procedure. However, change in BMI was not a significant predictor of improvement in asthma medication use on multivariate analysis for all types of bariatric surgery, so the type of surgery may have an impact on asthma-related outcomes.³³ The type of surgery has been shown to have a significant impact on resolution of diabetes even before the presence of a significant amount of weight loss.³⁴ Perhaps similar mechanisms underlying changes in metabolism are responsible for the disparate findings with regard to improvement in asthma following bariatric surgery. Further evaluation is warranted to determine the best procedure to recommend for a patient undergoing bariatric surgery with significant comorbid asthma.

WEIGHT MANAGEMENT AND IMPROVEMENT IN ASTHMA COMORBIDITIES

Both gastroesophageal reflux disease (GERD) and SDB are often comorbidities with asthma and possibly lead to worsening asthma severity. Treatment of these

conditions has been associated with improvements in asthma symptoms in some patients.^{35–38} Both GERD and obstructive sleep apnea are also associated with obesity and have been shown to improve with weight loss.^{22,23} Macgregor and Greenberg²¹ found that although GERD resolved after bariatric surgery in nearly all of the patients who clinically reported symptoms, there was no significant correlation with improvement in asthma, and some patients reported new-onset GERD after surgery and still had improvement in asthma.²² In a cohort of 257 patients undergoing bariatric surgery, presence of GERD before surgery similarly did not correlate with decreased asthma medication use. On the contrary, the presence of SDB correlated with decreased asthma medication use in univariate analysis but not multivariate analysis.³³ The only study to assess the effects of nonsurgical weight loss interventions on GERD and asthma showed improvements in asthma symptoms despite a lack of change in GERD symptoms.¹⁹ There is a lack of sufficient data to reach conclusions about whether reversal of GERD is the causative factor behind improvements in asthma control with weight loss.

WEIGHT LOSS AND MARKERS OF INFLAMMATION

Adipose tissue plays a key role in mediating systemic inflammation. Obesity results in increased levels of proinflammatory hormones and cytokines, including leptin, resistin, tumor necrosis factor alpha (TNF- α), and interleukin (IL)-6 (Table 2).^{5,6} The effect of weight loss on systemic inflammation has been shown in several studies, including a reduction in the expression of IL-4, a mediator of TH2 inflammation and other asthma-related gene expression following surgery. Johnson and colleagues¹⁶ noted that weight loss resulted in an improvement in markers of oxidative stress as well as TNF- α and brain-derived neurotrophic factor, which are known mediators of airway inflammation.^{6,39} Weight loss in this cohort was additionally associated with improved asthma control and AHR based on decreased variability of PEF. Other studies that evaluated markers of systemic inflammation found no association between weight loss and changes in inflammatory cytokine expression.^{12,17,32} It is unclear why weight loss results in variable responses with regard to cytokine expression; however, the study populations were heterogeneous with a variety of weight loss interventions, which may account for the difference. There are 2 studies that reported increases in adiponectin levels with weight loss regardless of whether the weight loss was achieved with surgical or nonsurgical interventions.^{20,32}

The correlation between clinical markers of airway inflammation in asthma including fraction of expired nitric oxide (Feno) and sputum eosinophilia has been examined to determine the effects of obesity on TH2 inflammation. Todd and colleagues⁴⁰ reported that BMI was not associated with sputum eosinophilia despite being increased in asthmatics in general. Feno is not correlated with changes in BMI, suggesting that obesity does not have significant effects on TH2 inflammation.⁴¹ These studies suggest that the effect of obesity may be mediated by non-TH2 inflammatory mechanisms. Weight loss has no effect on Feno expression^{20,31,33} or sputum eosinophilia.^{20,32,33} There are 2 studies that show improvements in sputum eosinophilia in a subset of patients.^{12,20} The reason for these differential responses has not been delineated but warrants further study. Innate and allergic airway inflammatory responses are likely altered by the presence of obesity and asthma. Dixon and colleagues³² reported increased cytokine production in stimulated peripheral T-cell cytokine 1 year after bariatric surgery. A study including patients not treated with inhaled corticosteroids yielded similar results, arguing against increased lymphocyte responses being related to decreased anti-inflammatory therapy.⁴¹

Table 2
Changes in inflammatory markers following weight loss via surgical and nonsurgical interventions

Study	Design	Population	Intervention	Measured	Changes
Johnson et al, ¹⁶ 2007	Prospective cohort	10 obese moderately persistent asthmatics	8-wk, alternating-day, low-calorie diet	TNF- α BDNP Markers of oxidative stress (8-isoprostane)	All with significant decrease
Maniscalco et al, ³⁰ 2008	Prospective cohort	22 obese asthmatic women	LAGB followed for 1 y	Feno	No significant change
Bafadhel et al, ¹² 2010	Observational	151 asthmatics	3 groups at 1 y (lost, maintained, or gained weight)	Feno Sputum eosinophils and neutrophils	No difference in Feno or sputum neutrophils. A decrease in sputum eosinophils in women but not in men who lost weight
Dixon et al, ³² 2011	Prospective	23 obese asthmatic 21 obese nonasthmatic	Bariatric surgery after 1 y	BAL and serum leptin and adiponectin BAL cell count Cytokine production from isolated CD4 cells	Decreased lymphocyte percentage on BAL with increased cytokine response from peripheral T cells No reduction in airway eosinophils No decrease of leptin but increase in BAL and serum adiponectin
Scott et al, ²⁰ 2013	Prospective	46 obese asthmatics	10 wk, diet, exercise, or combination	CRP IL-6 Serum leptin Serum adiponectin Sputum cell count	CRP, IL-6, and adiponectin were unchanged Sputum eosinophils improved in the exercise group only
Dias-Junior et al, ¹⁹ 2013	Open randomized trial	33 moderately obese asthmatics with severe asthma	22 diet and pharmacologic weight loss, 11 control at 6 mo	Feno Sputum cell count Serum CRP Serum leptin Serum eotaxin TGF β -1	There was no difference in any of the measured markers

Abbreviations: BAL, bronchoalveolar lavage; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; Feno, fraction of expired nitric oxide; TGF β -1, transforming growth factor beta-1.

SUMMARY

Although the heterogeneity in definitions of outcome, interventions, and study design make direct comparisons among the reviewed studies challenging, they all support the assertion that weight loss in obese subjects with asthma improves metrics of asthma control and in some cases lung function and AHR. More questions than answers remain and mechanistic studies designed to delineate the pathophysiologic changes that underlie the improvements in asthma control with weight loss are urgently needed.^{42–44}

Obesity is likely associated with 2 distinct phenotypes: one driven by traditional forms of TH2 inflammation in which obesity may be a consequence of underlying asthma and associated therapies, and the other that is driven by non-TH2 inflammation that is likely a consequence of the direct effects of obesity-related changes on inflammation.^{42,45} In the latter group, AHR may be mediated by mechanisms related directly to obesity, resulting in improvements in hyperresponsiveness with weight loss. It is this group of patients that is most likely to benefit from intensive weight loss strategies or bariatric surgery. Overall, weight loss seems to improve asthma symptoms, decrease medication use, and reduce exacerbations. Therefore weight management strategies should be discussed with overweight or obese patients who have asthma with poor control.

REFERENCES

1. Peters-Golden M, Swern A, Bird SS, et al. Influence of body mass index on the response to asthma controller agents. *Eur Respir J* 2006;27(3):495–503.
2. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;175(7):661–6.
3. de Oliveira Filho GR, Nicolodi TH, Garcia J, et al. Preanesthetic clinical problems of morbidly obese patients submitted to bariatric surgery: comparison with non-obese patients. *Rev Bras Anesthesiol* 2002;52(2):217–22.
4. Varraso R, Siroux V, Maccario J, et al. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005;171(4):334–9.
5. Boulet LP. Influence of obesity on the prevalence and clinical features of asthma. *Clin Invest Med* 2008;31(6):E386–90.
6. Sood A, Shore SA. Adiponectin, leptin, and resistin in asthma: basic mechanisms through population studies. *J Allergy (Cairo)* 2013;2013:785835.
7. Sood A, Dominic E, Qualls C, et al. Serum adiponectin is associated with adverse outcomes of asthma in men but not in women. *Front Pharmacol* 2011;2:55.
8. Lugogo NL, Bappanad D, Kraft M. Obesity, metabolic dysregulation and oxidative stress in asthma. *Biochim Biophys Acta* 2011;1810(11):1120–6.
9. Boulet LP, Tucotte H, Boulet G, et al. Deep inspiration avoidance and airway response to methacholine: Influence of body mass index. *Can Respir J* 2005;12(7):371–6.
10. Aaron SD, Vandemheen K, Boulet LP, et al. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179(11):1121–31.
11. Lugogo NL, Hollingsworth J, Howell DL, et al. Alveolar macrophages from overweight/obese subjects with asthma demonstrate a proinflammatory phenotype. *Am J Respir Crit Care Med* 2012;186(5):404–11.
12. Bafadhel M, Singapuri A, Terry S, et al. Body mass and fat mass in refractory asthma: an observational 1 year follow-up study. *J Allergy (Cairo)* 2010;2010:251758.

13. Haselkorn T, Fish J, Chipps B, et al. Effect of weight change on asthma-related health outcomes in patients with severe or difficult-to-treat asthma. *Respir Med* 2009;103(2):274–83.
14. Stenius-Aarniala B, Poussa T, Kvarnstrom J, et al. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000;320(7238):827–32.
15. Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. *Chest* 2000;118(5):1315–21.
16. Johnson JB, Summer W, Cutler RG, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radic Biol Med* 2007;42(5):665–74.
17. Hernandez Romero A, Matta Campos J, Mora Nieto A, et al. Clinical symptom relief in obese patients with persistent moderate asthma secondary to decreased obesity. *Rev Alerg Mex* 2008;55(3):103–11.
18. Aaron SD, Fergusson D, Dent R, et al. Effect of weight reduction on respiratory function and airway reactivity in obese women. *Chest* 2004;125(6):2046–52.
19. Dias-Junior SA, Reis M, de Carvalho-Pinto RM, et al. Effects of weight loss on asthma control in obese patients with severe asthma. *Eur Respir J* 2013;43(5):1368–77.
20. Scott HA, Gibson PG, Garg ML, 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(1):36–49.
21. Macgregor AM, Greenberg RA. Effect of surgically induced weight loss on asthma in the morbidly obese. *Obes Surg* 1993;3(1):15–21.
22. Dixon JB, Chapman L, O'Brien P. Marked improvement in asthma after Lap-Band surgery for morbid obesity. *Obes Surg* 1999;9(4):385–9.
23. Spivak H, Hewitt MF, Onn A, et al. Weight loss and improvement of obesity-related illness in 500 U.S. patients following laparoscopic adjustable gastric banding procedure. *Am J Surg* 2005;189(1):27–32.
24. Dhabuwala A, Cannan RJ, Stubbs RS. Improvement in co-morbidities following weight loss from gastric bypass surgery. *Obes Surg* 2000;10(5):428–35.
25. O'Brien PE, Dixon JB, Brown W, et al. The laparoscopic adjustable gastric band (Lap-Band): a prospective study of medium-term effects on weight, health and quality of life. *Obes Surg* 2002;12(5):652–60.
26. Brancatisano A, Wahlroos S, Brancatisano R. Improvement in comorbid illness after placement of the Swedish adjustable gastric band. *Surg Obes Relat Dis* 2008;4(3 Suppl):S39–46.
27. Hewitt S, Humerfelt S, Sovik TT, et al. Long-term improvements in pulmonary function 5 years after bariatric surgery. *Obes Surg* 2014;24(5):705–11.
28. Narbro K, Agren G, Jonsson E, et al. Pharmaceutical costs in obese individuals: comparison with a randomly selected population sample and long-term changes after conventional and surgical treatment: the SOS intervention study. *Arch Intern Med* 2002;162(18):2061–9.
29. Sikka N, Wegienka G, Havstad S, et al. Respiratory medication prescriptions before and after bariatric surgery. *Ann Allergy Asthma Immunol* 2010;104(4):326–30.
30. Maniscalco M, Zedda A, Faraone S, et al. Weight loss and asthma control in severely obese asthmatic females. *Respir Med* 2008;102(1):102–8.
31. Boulet LP, Turcotte H, Martin J, et al. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respir Med* 2012;106(5):651–60.

32. Dixon AE, Reis M, de Carvalho-Pinto RM, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011;128(3):508–15.e1–2.
33. Reddy RC, Baptist AP, Fan Z, et al. The effects of bariatric surgery on asthma severity. *Obes Surg* 2011;21(2):200–6.
34. Araia M, Wood M, Krool J, et al. Resolution of diabetes after bariatric surgery among predominantly African-American patients: race has no effect in remission of diabetes after bariatric surgery. *Obes Surg* 2014;24(6):835–40.
35. Puthalapattu S, Ioachimescu OC. Asthma and obstructive sleep apnea: clinical and pathogenic interactions. *J Investig Med* 2014;62(4):665–75.
36. Prasad B, Nyenhuis SM, Weaver TE. Obstructive sleep apnea and asthma: associations and treatment implications. *Sleep Med Rev* 2014;18(2):165–71.
37. Kiljander TO, Laitinen JO. The prevalence of gastroesophageal reflux disease in adult asthmatics. *Chest* 2004;126(5):1490–4.
38. Chan WW, Chiou E, Obstein KL, et al. The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis. *Arch Intern Med* 2011;171(7):620–9.
39. Lommatzsch M, Schloetcke K, Klotz J, et al. Brain-derived neurotrophic factor in platelets and airflow limitation in asthma. *Am J Respir Crit Care Med* 2005;171(2):115–20.
40. Todd DC, Armstrong S, D'Silva L, et al. Effect of obesity on airway inflammation: a cross-sectional analysis of body mass index and sputum cell counts. *Clin Exp Allergy* 2007;37(7):1049–54.
41. McLachlan CR, Poulton R, Car G, et al. Adiposity, asthma, and airway inflammation. *J Allergy Clin Immunol* 2007;119(3):634–9.
42. Sideleva O, Black K, Dixon AE. Effects of obesity and weight loss on airway physiology and inflammation in asthma. *Pulm Pharmacol Ther* 2013;26(4):455–8.
43. Adeniyi FB, Young T. Weight loss interventions for chronic asthma. *Cochrane Database Syst Rev* 2012;(7):CD009339.
44. Moreira A, Bonini M, Garcia-Larsen V, et al. Weight loss interventions in asthma: EAACI evidence-based clinical practice guideline (part I). *Allergy* 2013;68(4):425–39.
45. Lugogo NL, Kraft M, Dixon AE. Does obesity produce a distinct asthma phenotype? *J Appl Physiol* (1985) 2010;108(3):729–34.