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Obesity, metabolic dysregulation and oxidative stress in asthma

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Abstract

Background—Epidemiological data demonstrate an increased risk of developing incident asthma with increasing adiposity. While the vast majority of studies support the interaction between obesity and asthma, the causality is unclear.

Scope of review—This article will review the current literature supporting the presence of an obese asthma phenotype and the possible mechanisms mediating the effects of obesity on asthma.

Major conclusions—Obesity is associated with poor asthma control, altered responsiveness to medications and increased morbidity. Obesity is characterized by systemic inflammation that may result in increased airway inflammation. However, this assertion is not supported by current studies that demonstrate a lack of significant airway inflammation in obese asthmatics. In spite of this observation one must consider limitations of these studies including the fact that most subjects were treated with inhaled corticosteroids that would likely alter inflammation in the lung. Thus, it remains unclear if obesity is associated with alterations in inflammation in the airways of subjects with asthma.

Hormones such as leptin and adiponectin are affected by obesity and may play a role in mediating innate immune responses and allergic responses, respectively. The role of oxidative stress remains controversial and the current evidence suggests that while oxidative stress is important in asthma, it does not fully explain the characteristics associated with this unique phenotype.

General significance—Obesity related asthma is associated with increased morbidity and differential response to asthma therapies. Understanding the mechanisms mediating this phenotype would have significant implications for millions of people suffering with asthma. This article is part of a Special Issue entitled Biochemistry of Asthma.

Keywords

Asthma; Obesity; Metabolic syndrome; Oxidative stress; Leptin; Inflammation

1. Introduction

The incidence of obesity in the United States is striking and currently 30% of the adult population is considered obese [1]. Obesity is now an epidemic with significant public health implications. Obesity is associated with an increased risk of developing diabetes, coronary artery disease and non-alcoholic steatohepatitis [2]. Numerous epidemiologic studies published during the past decade have demonstrated an increased risk of asthma

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associated with increasing obesity [3–5]. The effect of obesity on the occurrence of asthma is more prominent in women [6–8] and there is a dose response effect of increasing body mass index (BMI) on asthma incidence [3]. The increased risk of obesity on the occurrence of asthma is most prominent in non-allergic individuals [9,10].

Asthma is primarily characterized by T-helper (TH2) mediated inflammation, however, it has recently been recognized that non-TH2 cytokines like interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α) may play a role in asthma pathogenesis [11]. Exhaled nitric oxide is an accepted marker of TH2 inflammation in asthma and its expression is increased in allergic asthma. Several studies have demonstrated an inverse relationship between obesity and exhaled nitric oxide levels [9,10,12,13] further supporting the assertion that the interaction between obesity and asthma is not primarily mediated by classical, allergic (TH2) inflammation.

Postulated mechanisms for the increased risk of asthma associated with obesity include changes in airway smooth muscle stretch due to the presence of shallow breathing associated with obesity, effects of gastroesophageal reflux, inaccurate diagnosis of asthma, sleep disordered breathing, genetic polymorphisms and the effect of systemic adipocytokines and oxidative stress on both pulmonary and extra-pulmonary inflammation [14–18].

Adipose tissue is now recognized as metabolically active, playing a role in the regulation of energy homeostasis and has significant pathological effects that result in many obesity-related diseases. The role of white adipose tissue in mediating systemic inflammation is an area of active investigation in both cardiac disease and diabetes. Adipose tissue is infiltrated by bone-marrow derived macrophages that secrete adipokines and cytokines in the systemic circulation resulting in a chronic inflammatory state [19]. Obesity is associated with increased leptin and resistin (pro-inflammatory hormones) and decreased adiponectin, a hormone with potent anti-inflammatory effects. Additionally, there are increased levels of circulating cytokines including TNF- α , interleukin (IL)-6, monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF) [20,21]. These cytokines propagate inflammation and angiogenesis. Low serum IL-10 levels result in a vicious cycle of increased inflammation that is unabated. The effect of systemic inflammation on metabolic dysregulation is clear and supported by strong evidence. The role of systemic inflammation, adipocytokines and oxidative stress in mediating the obese asthma phenotype is unclear (Table 1).

It is becoming increasingly evident that obesity is associated with a unique asthma phenotype that is characterized by more severe disease with variable response to conventional asthma therapies. Despite this, caution must be taken when assessing obese asthmatics. It seems more plausible that obese asthmatics will fall into various phenotypes including those with allergic/atopic asthma and those with predominantly non-allergic characteristics. The latter phenotype is likely an adult onset female-predominant group with non-atopic disease [22]. More sophisticated phenotypic characterizations are essential in determining biomarkers that would improve understanding of the complex interaction between obesity and asthma.

1.1. Obesity and asthma severity

Obesity is associated with increased asthma severity in both children and adults [10,23–26]. Taylor et al. determined that obesity is associated with increased daily asthma symptoms, missed workdays, increased rescue bronchodilator usage and increased asthma severity as determined by GINA guidelines. This association was present even after adjusting for age, gender, race, income, education level, employment status, family history and residence [27]. Obese asthmatics have a higher risk of hospitalization (OR 4.6) for acute asthma

exacerbations [28] and have poorer quality of life [29]. Concurrent with more severe disease is a poor response to conventional asthma therapies.

2. Obesity and variable treatment response

Obesity is associated with decreased glucocorticoid responsiveness associated with an inability to achieve adequate asthma control both with inhaled corticosteroids and combination therapies that include inhaled corticosteroids and long acting bronchodilators [30–34](Table 2).

Multiple studies have found a blunted response to corticosteroids in overweight and obese asthmatics. Peters–Golden et al. performed a *post hoc* analysis of four double blind, placebo controlled studies randomizing 3073 moderate asthmatics to beclomethasone, montelukast or placebo with the primary endpoint of asthma control days. These studies demonstrated that the response to inhaled corticosteroids inversely correlated with increasing BMI. However, a similar treatment response to montelukast, a leukotriene antagonist, was seen in asthma, regardless of BMI [35].

Boulet and Franssen performed a retrospective analysis of patients enrolled in five double-blind studies that randomized 1242 moderate asthmatics to fluticasone versus fluticasone/salmeterol with asthma control as the primary outcome. They found that obese patients were less likely than non-obese patients to achieve asthma control with either fluticasone or fluticasone/salmeterol [30]. Forno et al. also performed a retrospective analysis examining 1041 children randomized to budesonide vs. placebo/nedocromil with improved lung function as the primary outcome. Overweight and obese children had less response to budesonide compared to non-overweight children [36].

The mechanisms that mediate the differential treatment response to corticosteroids are unknown. Sutherland et al. proposed decreased mitogen-activated protein kinase phosphatase-1 (MKP-1) expression in peripheral blood mononuclear cells (PBMCs) and lung cells (likely macrophages) [33]. Up regulation of MKP-1 is important in mediating the anti-inflammatory effects of dexamethasone via inactivation of pro-inflammatory signaling. Thus, they proposed that the reduced expression of MKP-1 was associated with reduced clinical corticosteroid responsiveness. Additionally, obese asthmatics also demonstrated increased PBMC TNF- α expression that correlated with increasing BMI. The presence of increased TNF- α levels may result in alterations in the inflammatory profile in the lungs of obese asthmatics and alter response to glucocorticoids.

Other postulated mechanisms for the variable response to therapy include the assertion that obesity has effects on asthma control mediated by obesity related changes in lung mechanics [37]. Additional proposed mechanisms include the potential role of vitamin D deficiency on glucocorticoid responsiveness. Vitamin D deficiency is more common in obese individuals as demonstrated by Sutherland et al. who found an inverse relationship between vitamin D levels and BMI [38]. More importantly, low vitamin D levels are associated with decreased glucocorticoid responsiveness in asthma [38].

The role of leukotriene (LT) antagonists in the treatment of obese patients with asthma is unclear. Increased 5-lipoxygenase activating protein and LTB₄ levels have been demonstrated in the adipose tissue of obese mice [39]. In addition, macrophage infiltration and free fatty acid secretion is increased in parallel to changes in 5-lipoxygenase activating protein levels [39]. Adipose tissue incubated with 5-lipoxygenase products results in increased nuclear factor kappa beta (NF- κ B) activation and secretion of pro-inflammatory cytokines including TNF- α , MCP-1 and IL-6, an effect that is ameliorated by the addition of 5-lipoxygenase activating protein inhibitors [39,40]. Leung et al. noted increased exhaled

nitric oxide and urinary LTB₄ levels in children with asthma. However these inflammatory markers were not affected by obesity status [41].

The role of leukotrienes and 5-lipoxygenase in asthma is well accepted and the beneficial effects of therapy with 5-lipoxygenase inhibitors and leukotriene antagonists are clear [42–44]. However, the role of leukotrienes and 5-lipoxygenase in modulating the effects of obesity in asthma remains controversial and warrants further investigation. If these mediators are prominent contributors to inflammation in the lungs of obese asthmatics, then there would be potential treatment implications. Specifically, leukotriene antagonists and 5-lipoxygenase inhibitors would be considered more targeted treatments in obese asthmatics and thus would be more widely used in this population.

Human studies focused on delineating the impact of leukotrienes and 5-lipoxygenase inhibitors on asthma control in obese asthmatics are all retrospective and have yielded conflicting results. Prior studies noted improvements in asthma control with leukotriene antagonist therapy in obese asthmatics, without any differential effects of obesity on response to therapy with leukotrienes [31]. However, a recent retrospective analysis by Sutherland et al. suggested that fluticasone was more effective than montelukast at achieving asthma control, irrespective of body mass index [45,46]. Combination therapy with fluticasone and salmeterol resulted in greater treatment response (based on FEV₁, asthma symptom scores and albuterol usage) than montelukast in obese asthmatics. Conversely, in a study by Camargo et al., lean asthma subjects had a greater treatment response to combination therapy and montelukast as defined by improvement in FEV₁, asthma symptom scores and albuterol usage as compared to obese asthmatic subjects [46].

Although there are conflicting data regarding the role of 5-lipoxygenase and leukotrienes in the pathogenesis of asthma in obese persons, there is some scientific rationale for potential effects of these mediators in the obesity-asthma interaction. Therefore, further research is required to determine the role of these mediators in affecting both asthma pathogenesis and response to treatment in obese asthmatics. Prospective studies comparing effectiveness of the addition of leukotriene antagonists and 5-lipoxygenase inhibitors to inhaled corticosteroid therapy on achieving and maintaining asthma control in obese asthmatics are warranted.

Thus far, there is mounting evidence that supports the assertion that obesity results in a unique asthma phenotype that requires further characterization and more importantly, a focus on alternative therapies [47].

3. Metabolic dysregulation, systemic and airway inflammation and asthma

The National Heart Lung Blood Institute and American Heart Association define the metabolic syndrome as a syndrome that includes abdominal obesity, arterogenic dyslipidemia, elevated blood pressure, insulin resistance or impaired glucose tolerance, a pro-inflammatory state and a pro-thrombotic state [48]. The metabolic syndrome is associated with an increased risk of diabetes, cardiovascular disease, sleep apnea, asthma and certain malignancies. Leone et al. found an association between impaired lung function and metabolic syndrome regardless of BMI and predominately due to central adiposity [49]. This association persisted after exclusion of patients with a prior history of lung disease. Similar results were reported in prior studies that demonstrated an association between lung function impairment and metabolic syndrome [50,51]. The authors did not specifically focus on asthma in this cohort; however prior studies have found an increased risk of asthma associated with obesity. One can postulate that common pathways underlie lung function impairments and development of metabolic syndrome.

The presence of systemic inflammation as characterized by an elevated C-reactive peptide (CRP) level is well accepted as part of the metabolic syndrome [52]. The effect of systemic inflammation on airway inflammation in asthma is controversial. Most studies have found no association between obesity and increased airway inflammation in asthma [53–56]. A prospective study by Sutherland et al., demonstrated increased IL-1, IL-5, IL-6 and IL-8 in sputum supernatants of asthmatics, however no differences were noted between obese and lean asthmatics leading the authors to conclude that the obese asthma phenotype is not a result of changes in airway inflammation [57]. Dixon et al. studied a cohort of patients with asthma who underwent bariatric surgery. There was a significant improvement in asthma symptoms and lung function with weight loss but no change in airway inflammation as characterized by bronchoalveolar lavage and induced sputum cell counts [58]. These studies suggest that airway inflammation and classical TH-2 driven inflammation does not mediate the variable response to therapy, increased symptoms and decreased asthma control seen in obese asthmatics. Although these results are interesting, the majority of subjects included by in both studies were taking an inhaled corticosteroid and this may have altered the inflammatory profile in the lung. The report by Dixon et al. did not include the measurements of cytokines in bronchoalveolar lavage fluid and therefore differences in inflammation may not have been elucidated. The compartments of the lung sampled by sputum and bronchoalveolar lavage differ making comparisons between the two studies more challenging. Despite the findings in these two studies, conclusions regarding whether inflammation in asthmatics differs based on obesity should be reserved until further evidence is obtained.

4. Oxidative stress in obesity and the effect on asthma

Oxidative stress is characterized by the presence of increased reactive oxygen species (ROS) either as a result of increased production of ROS or decreased amounts of antioxidants present. Reactive oxygen species create a variety of pathologic changes in the airways including increased airway reactivity and increased mucous production, factors that have important implications in asthma. Obesity is associated with increased oxidative stress and systemic inflammation [59,60]. Increased systemic or airway oxidative stress may be a potential mechanism by which obesity results in increased asthma severity. Assessment of oxidative stress can be made through direct measurement of reactive oxygen species or indirect measurement of the oxidative products in either plasma or exhaled breath condensate (EBC).

Asthma is associated with increased exhaled breath condensate levels of malondialdehyde (MDA) and reduced glutathione, both demonstrated in children [61,62]. Glutathione, in its reduced form, protects airway epithelial cells from free radicals while MDA is formed due to the action of reactive oxygen species on membrane phospholipids and is a marker of oxidative stress. Plasma MDA levels are increased and glutathione levels are decreased in children with asthma, with the highest levels of oxidant stress occurring in children with more severe disease [63]. Epithelial lining fluid levels of anti-oxidants are significantly lower in children with severe asthma indicating the presence of oxidative stress [64]. These alterations in oxidative stress occur independent of BMI and appear to be indicative of disease activity. Exhaled breath 8-isoprostane levels are increased in the children with asthma, however the effect of obesity was not delineated [65]. Oxidant–antioxidant imbalance plays an important role in asthma; however, the effects of obesity are unknown in children.

In adults, the available data are contradictory. The current studies reveal distinct differences in plasma and exhaled levels of oxidative markers that are not concordant and thus difficult to interpret. Increased plasma 8-isoprostane levels have been noted in asthma. However this

association is not present after adjusting for obesity. This suggests that the elevated plasma levels are a consequence of obesity rather than asthma [66]. Conversely, Komakula et al. demonstrated an association between increased exhaled 8-isoprostane levels and BMI but only in asthmatics [67]. Interestingly, the level of exhaled 8-isoprostanes did not differ between asthmatics and normal controls. The asthma subjects demonstrated an inverse correlation between exhaled nitric oxide (NO) and BMI. In this study, serum levels of adipokines (leptin and adiponectin) did not correlate with changes in markers of oxidative stress. The authors proposed that obesity was associated with increased oxidative stress, but only in asthma. The decreased exhaled NO levels were thought to result from changes in baseline NO redox metabolism and conversion of the NO present in the airway to reactive nitric oxygen species [67]. Furthermore, the authors postulated that increased oxidative stress in the lung might be due to increased leptin levels that occur with obesity. Leptin has been shown to increase oxidative stress in endothelial cells by increasing NF- κ B activation in an oxidant dependent manner [68]. The role of leptin in inducing increased oxidative stress in the lungs of obese asthmatics is unknown.

The current data support the assertion that asthma is associated with increased oxidative stress. However, it is unclear if the presence of increased airway oxidative stress is a consequence of changes in systemic oxidative stress seen in obesity. To determine the association between airway and systemic oxidative stress, Holguin et al. measured serum and exhaled 8-isoprostane levels in a cohort of moderate to severe adult asthmatics. The presence of obesity, but not asthma, was associated with increased exhaled 8-isoprostane levels. Conversely, plasma levels of 8-isoprostanes were higher in asthmatics but there was no effect of obesity noted [18]. In addition, there was no correlation between exhaled and plasma 8-isoprostane levels [18]. Based on these data, the authors inferred that while asthma increases systemic oxidative stress and obesity increases airway oxidative stress there was no synergism between plasma and exhaled 8-isoprostane levels.

The discordance in the exhaled as compared to plasma level of 8-isoprostanes has led to challenges in delineating the role of oxidative stress in obese asthmatics and more importantly, the use of 8-isoprostanes as a reliable marker of variability in oxidative stress. It is plausible that oxidative stress may not be a causative factor but rather may modulate asthma severity and alter response to medications. The authors further inferred that although baseline levels of inflammation did not differ, response to exacerbating factors might be more robust in obese asthmatics with propagation of oxidative stress that results in more severe symptoms and prolonged episodes of poor asthma control [18]. Conclusions regarding the role of oxidative stress in obese asthmatics are difficult to make given the conflicting data that are available at this time.

5. The role of adipokines in obesity related asthma

Obesity is associated with increased serum leptin levels that may be associated with increased inflammation in the airways of obese asthmatics [11]. Leptin has been shown to regulate T-cell proliferation and activation, to recruit and activate macrophages and promote angiogenesis [55,69]. Studies assessing the role of leptin in human asthma are limited. Guler et al. noted that serum leptin was predictive of asthma in boys, even after adjusting for BMI [70]. Other studies reveal higher leptin levels in asthmatic women compared to non-asthmatic women. However, adjusting for serum leptin levels does not affect the association between BMI and asthma [71]. One can postulate that leptin, a potent pro-inflammatory hormone, may promote increased non-TH2 airway inflammation, a mechanism that has not been studied extensively in humans. In mouse models of asthma, leptin augments airways hyperresponsiveness (AHR) but a lack of leptin does not completely attenuate AHR

indicating that leptin does not entirely explain the presence of increased AHR in obese mice [72–74]. Leptin also augments ozone-induced inflammation in obese mice [73].

Recently, several studies in humans have not demonstrated significant differences in inflammation in the airways of obese asthmatics in spite of differences in disease characteristics [57,58]. However, as previously discussed, there are limitations with these studies that affect our ability to draw concrete conclusions about the presence of inflammation in the airways of obese asthmatics. We propose that leptin may play both a pro-inflammatory and immune modulating role in obese asthmatics, thus contributing to this unique phenotype (Fig. 1).

Adiponectin is a 30 kDa protein with an N-terminal collagenase domain followed by a C-terminal globular domain. It exists in both low molecular weight and high molecular weight forms [75]. Adiponectin has primary effects on energy metabolism and its effects are anti-diabetic in nature. It also has many anti-inflammatory effects and inhibits the production of the pro-inflammatory cytokines IL-6 and TNF- α [76] while inducing the anti-inflammatory cytokines IL-1 receptor antagonist and IL-10 [77–79]. Serum adiponectin and IL-10 levels are lower in obesity [80] and increase with weight loss [81–84]. Interestingly, adiponectin can have pro-inflammatory effects depending on the stimulus present [21]. Adiponectin markedly attenuates allergen induced airway inflammation in mice [85] and adiponectin deficient mice demonstrate greater eosinophilia [86]. In premenopausal women serum adiponectin levels are protective against the development of asthma [87]. A study assessing the effects of allergen challenge on serum adiponectin levels in asthmatics did not reveal any correlation leading the authors to conclude that adiponectin may not play a role in the acute allergen response in humans [88]. Adiponectin resistance and deficiency may play a role in propagating unabated inflammation in the obese patient with asthma. However, further studies are warranted to determine its role in humans. The data obtained from mouse models are promising but lack of translation to human obesity is a concern and is most likely due to a complex interaction of several pro and anti-inflammatory adipokines.

One potential way to evaluate the role of adiponectin on asthma control in obese asthmatics would be to evaluate the impact of thiazolidinediones (TZDs) on asthma control. TZDs increase serum adiponectin levels [75] and the higher adiponectin levels could have potential anti-inflammatory effects in the lung. Furthermore, mechanistic studies in humans are needed to determine the role of adiponectin in ameliorating inflammation in various cell types obtained from the lungs of asthmatics.

6. Effects of weight loss on obese asthmatics

The obese asthma phenotype can be reversed by weight loss with improvements in lung function, asthma control and asthma severity with decreased medication utilization and hospitalizations [16,58,89–92]. Even modest dietary alterations can result in decreased markers of oxidative stress and inflammation in overweight patients with moderate asthma [93]. Prospective studies to determine the etiology of these improvements in asthma are necessary and will provide invaluable insights into the pathophysiology of asthma in obesity. Moreover, despite the lack of a clear mechanism, the beneficial effects of weight loss appear to be unequivocal and thus weight management strategies should be included in the management of the obese asthmatic.

7. Conclusions

Numerous studies have demonstrated a strong association between obesity and asthma however the direction of causality is unclear. The current evidence supports the finding that obese asthmatics have more severe disease and variable treatment response. Additionally, it

is becoming increasingly evident that there is heterogeneity within this population of obese asthmatics. There may in fact be several distinct obese asthma phenotypes based on the presence or absence of atopy. The interaction between obesity and asthma is complex and there are several potential mechanisms that mediate the recognized clinical phenotype. Further studies are desperately needed to delineate the mechanism that mediates the clinical phenotype and more importantly, to help guide future therapeutic targets for this unique, but common asthma phenotype.

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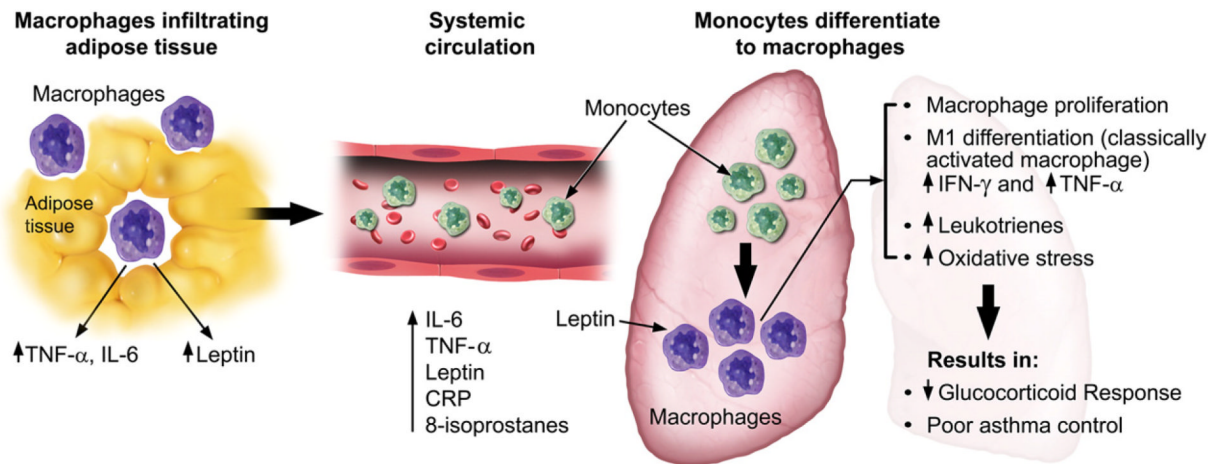


Fig. 1. Adipose tissue in obese subjects produces pro-inflammatory cytokines that result in systemic inflammation with increased circulating levels of IL-6, TNF- α , and leptin. Circulating monocytes are recruited into the lung where they differentiate into macrophages. Leptin plays a key role in macrophage proliferation and differentiation in the lung with subsequent secretion of pro-inflammatory cytokines. Additionally obese asthmatics may have increased oxidative stress and leukotriene synthesis. These alterations in pathophysiology result in poor asthma control and decreased glucocorticoid response.

Table 1

Studies assessing the effects of obesity on asthma severity.

Study	Design	Patient population	Analysis	Results
Von Mutius 2001	Cross sectional analysis	7505 children age 4-17	Multivariate regression	Prevalence for asthma increased with BMI
Akerman 2004	Retrospective chart analysis	143 adults at single academic medical center	Spearman correlation coefficients	Prevalence of obesity increased with increasing asthma severity
Blanden 2004	Prospective, observational surveys	100 children age 7-17	Central tendency, standard deviation, and standard error	Obese patients with decreased QOL compared to normal weight patients with asthma
Cassol 2006	Cross sectional analysis	4010 children age 13-14	Chi-square test and odds ratio	Positive association between obesity and both asthma prevalence and severity
Taylor 2008	Cross sectional analysis	3095 adults	Multivariate regression analysis	Positive association between obesity and asthma severity and control
Mosen 2008	Cross sectional	1113 adults	Multiple logistic regression models	Positive association between obesity and worse asthma control and increased risk of asthma related hospitalizations

Table 2

Studies assessing the response to asthma controller medications in obese asthma subjects.

Study	Design	Patient population	Intervention	Primary endpoint	Results
Dixon 2006	Retrospective analysis	488 moderate asthmatics	Theophylline vs montelukast vs placebo	Asthma control	Increased asthma exacerbations in obese patients treated with theophylline but no difference in response to LTRA
Peters Golden 2006	Retrospective analysis	3073 moderate asthmatics	Beclamethasone vs montelukast vs placebo	Asthma control days	Decreased response to ICS with increasing BMI
Boulet and Franssen 2007	Retrospective analysis	1242 moderate asthmatics	fluticasone vs fluticasone/salmeterol	Asthma control	Obese patients less likely than non-obese to achieve asthma control with either
Sutherland 2009	Cross sectional study	1265 moderate asthmatics	variable	Treatment response	Overweight and obese had smaller improvements in lung function but no difference in response to LTRA
Sutherland 2010	Retrospective analysis	1052	Fluticasone vs montelukast	FEV ₁	Greater FEV ₁ improvement with fluticasone vs montelukast
Carmago 2010	Retrospective analysis		Fluticasone/salmeterol vs montelukast	Treatment response	Greater treatment response to FP/ Salmeterol than montelukast
Forno 2011	Retrospective analysis	1041 mild to moderate asthmatics	Budesonide vs placebo or nedocromil	Lung function	Overweight and obese children had less response to budesonide
Farah 2011	Cross sectional study	49 moderate asthmatics	Budesonide	Treatment response	Asthma control, spirometry and airway inflammation improved similarly