Obesity and asthma: cause for concern
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Epidemiological data indicate that obesity is a risk factor for incident asthma, and that obesity is also associated with increased asthma severity. Importantly, obesity antedates asthma. The observations that weight loss improves asthma and that obese mice have innate airway hyperresponsiveness and increased responses to asthma triggers also support a relationship between obesity and asthma. The basis for this relationship is unknown, but might be the result of common etiologies, comorbidities, effects of obesity on lung volume or adipokines. Understanding the mechanistic basis for the relationship between obesity and asthma could lead to new therapeutic strategies for treatment of this susceptible population.

Introduction
Obesity is an important public health problem both in the USA (http://www.cdc.gov/nccdphp/dnpa/obesity/trend/index.htm) and worldwide [1]. It is well established that obesity increases the risk of cardiovascular disease, type 2 diabetes and some forms of cancer. There are now strong epidemiological data indicating that obesity is also a risk factor for asthma. These data include both cross-sectional and prospective studies, and are supported by studies demonstrating effects of weight loss or weight gain on a variety of asthma outcomes. Data from animal models also support a relationship between obesity and asthma. The basis for this relationship remains to be established but prospective studies clearly demonstrate that obesity antedates asthma. It is possible that obesity and asthma share some common etiology, such as a common genetic basis, but there are also other plausible biological mechanisms whereby obesity could be expected to either cause or worsen asthma. These include co-morbidities such as gastroesophageal reflux disease (GERD) and complications from sleep-disordered breathing (SDB), effects of obesity on lung volume and breathing pattern, and endocrine factors, including adipose-derived cytokines, chemokines and hormones. The purpose of this review is to summarize and evaluate both the human and animal data supporting a relationship between obesity and asthma and to discuss what is known about the mechanistic basis for this relationship.

Epidemiology of obesity and asthma
The first reports of an association between obesity and asthma came from two large surveys in the 1980s examining the impact of being overweight or obese on the prevalence of chronic diseases. Since then, more than 30 cross-sectional and case-control studies on this topic have been reported. The reader is referred to two recent reviews for a complete listing of these studies [2,3]. Almost without exception, these studies report an increased prevalence of asthma in obese and/or overweight children, adolescents and adults of multiple nationalities and ethnic groups throughout the world; however, they do not address the direction of causality. Indeed, one interpretation of these studies is that asthma leads to obesity, perhaps because asthmatics adopt a sedentary life style to avoid respiratory symptoms during exercise. However, results from more than a dozen prospective studies in adults and children (cited by Shore and Johnston [3]) indicate that this is not the case. Each of these studies, which involved thousands of individuals, with follow-up periods varying from 2–21 years, reported an increased incidence of asthma in the obese and overweight, and demonstrated that obesity antedates asthma. Some studies have indicated a greater effect of obesity in females than in males, although the results have not been consistent [3]. For example, the most recent prospective study in children indicates an increased risk of incident asthma in obese boys but not girls [4].

The first prospective analysis of the relationship between obesity and asthma came from the Nurses’ Health Study and examined the relationship between body mass index (BMI) and the risk of new-onset asthma over four years in more than 86 000 adult women who were free of asthma at the start of the study [5]. Incident asthma, based on self-reports of a doctor’s diagnosis, was assessed by questionnaire. Subjects were grouped according to BMI calculated from self-reported height and weight assessed at the start of the study. This initial BMI showed a positive dose–response association with the risk of new asthma, with a relative risk of 2.6 for obese subjects (those with a BMI ≥30) after adjustment for important cofactors.
Obesity and asthma: cause for concern

The largest prospective study examined over 135,000 Norwegian men and women [6**]. Subjects who initially did not have asthma were followed for an average of 21 years. New asthma was self-reported, and height and weight were measured before the development of asthma. The incidence of asthma increased at a rate of 10% and 7% per unit increase in BMI in men and women, respectively. Although both of these studies [5,6**] found a linear relationship between the relative risk for incident asthma and BMI, several other studies have described either a J-shaped or U-shaped relationship [3], indicating that extreme thinness is also a risk factor for asthma. The basis for the effect of low BMI is not known but might reflect nutritional deficits that have an impact on asthma.

The major criticism of these studies has been the use of self-reports of a doctor’s diagnosis of asthma. The concern is that asthma is misdiagnosed in the obese and that apparent symptoms of asthma actually reflect dyspnea upon exertion, resulting from poor conditioning or increased work of breathing. Data countering this argument are, firstly, that in some studies [7–9], asthma cases were confirmed by peak flow variability, response to a bronchodilator or airway airway hyperreactivity (AHR). Secondly, in other studies [5,10–12], the obesity-related relative risk of asthma was unchanged or even increased when increasingly stringent criteria, including use of bronchodilators or corticosteroids, were used to ascertain cases of incident asthma. The likelihood that asthma diagnosed in the obese reflects true asthma is also supported by the study of Thomson et al. [13], who reported that obese asthmatics seeking emergency room care for their asthma had marked airway obstruction and responded to a regimen of bronchodilators and corticosteroids with improvements in pulmonary function similar to those of non-obese asthmatics.

In addition to its role as a risk factor for incident asthma, obesity appears to increase asthma severity. Compared with lean asthmatics, obese asthmatics have more missed school days per year, a lower peak expiratory flow, more prescribed asthma medications and more emergency room visits [14]. Based on a retrospective medical record review of patient records at an inner-city academic asthma center, Akerman et al. [15] reported a linear relationship between asthma severity and BMI. Similarly, Varraso et al. [16] found a relationship between clinical asthma severity score and BMI — but only in women. Asthma is also more difficult to control in the obese [17]. By contrast, Tantisira et al. [18] were unable to demonstrate an association between obesity and asthma severity in children, although their population consisted of mostly mild asthmatics.

A few studies have examined the relationship between BMI and atopy but the data are inconsistent. In some studies, obesity was associated with asthma but not with other atopic diseases [19**]. In others [10,20], a relationship between obesity and asthma was observed only in non-atopic asthmatics. However, other investigators have found increases in atopy with obesity, although positive associations appear to have been confined to female subjects and mostly to children [7,21].

With respect to other asthma phenotypes, some investigators have reported the presence of reversible airflow obstruction in obese asthmatics [7,22], although remarkably few have actually measured it. Some investigators have reported a relationship between obesity and AHR but the relationship is not consistently observed (for details, see Shore and Johnston [3]). Reports of the inflammatory profile of the airways of obese asthmatics are virtually nonexistent. This remains a large and important gap in our knowledge of the phenotype of the obese asthmatic.

Weight change studies

Both weight loss and weight gain have been shown to have an impact on asthma. The impact of weight gain has been examined in four studies, two in adults [5,11] and two in children [7,23]. In each, the effect of weight gain was substantial. For example, in the Tuscon Children’s Respiratory Health Study, girls who became obese between the ages of six and 11 years had an almost fivefold increased risk of developing new asthma symptoms compared with girls who remained lean [7].

Studies of surgically induced weight reduction report significant improvements in all asthma outcomes, including prevalence, severity, use of asthma medications and hospitalizations for asthma [24,25*]. Studies of diet-induced weight loss also support a beneficial effect of weight loss on airway function in obese asthmatics [22,26,27]. For example, obese asthmatics who took part in a weight reduction program that involved a very low calorie diet achieved a 14–15% reduction in body weight that was associated with increases in peak expiratory flow, forced expiratory volume in one second and forced vital capacity, as well as reductions in dyspnea score and use of rescue medications [26]. A major concern with these diet-induced weight loss studies is that the number of subjects involved is small. Another concern is that, in addition to reductions in energy intake, there might have been changes in dietary composition that affected lung function.

Animal studies

Obese mice have been used to model the relationship between obesity and asthma. These studies have examined the impact of obesity on innate AHR, as well as on responses to common asthma triggers, such as ozone (O3) and allergen. Mice used in these studies included ob/ob mice, which are genetically deficient in the satiety hormone, leptin; db/db mice, which are genetically deficient...
in the leptin receptor isoform that is important for satiety; Cpe\textsuperscript{fat} mice, which are genetically deficient in carboxypeptidase E (Cpe), an enzyme involved in processing neuropeptides involved in satiety; and mice with diet-induced obesity (DIO) resulting from a high-fat diet.

Ob/ob, db/db and Cpe\textsuperscript{fat} mice each have innate AHR to intravenous methacholine [28,29**,30]. We have also observed innate AHR in mice with DIO (Johnston et al., unpublished). These data indicate that AHR is independent of the modality of obesity. AHR is also observed in obese mice when 5-hydroxytryptamine, rather than methacholine, is used as the bronchoconstricting agonist [30]. Non-specific AHR to multiple agonists is also a feature of human asthma.

O\textsubscript{3} is the major component of photochemical smog and is an important asthma trigger. Obese mice are more responsive than lean mice to acute inhalation of O\textsubscript{3}. O\textsubscript{3} exposure increases pulmonary resistance and airway responsiveness to a greater extent in obese than in lean mice, regardless of the modality of obesity [28,29**,30]. O\textsubscript{3}-induced increases in the concentrations of several bronchoalveolar lavage inflammatory markers are also greater in obese versus lean mice [28,29**,30].

An interesting aspect of the lung biology of ob/ob and db/db mice is their small lung size. These mice have substantially reduced lung volumes and decreased lung mass [28,30], whereas obese Cpe\textsuperscript{fat} mice do not [29**]. The reason for the small lung size is not known. Because ob/ob and db/db mice lack either leptin or the long form of the leptin receptor, whereas serum leptin is elevated in Cpe\textsuperscript{fat} mice, it is possible that leptin is important for lung growth. Alternatively, reductions in thoracic volume secondary to increased abdominal mass or accumulation of intrathoracic fat might limit lung growth and development in ob/ob and db/db mice. These mice become obese very early in life, whereas obesity develops more slowly in Cpe\textsuperscript{fat} mice, perhaps after the crucial phases of lung development. In any event, it is unlikely that these differences in lung size contribute substantively to the innate AHR or to the increased responses to O\textsubscript{3} that are observed in ob/ob and db/db mice because these changes in responsiveness are also observed in Cpe\textsuperscript{fat} mice [29**].

Obesity and/or dietary constituents elevated in obesity can also augment certain responses to allergen challenge. Mito et al. [31] examined the effect of DIO on responses to allergen challenge in the lung. In the absence of ovalbumin (OVA) sensitization and challenge, splenocytes from mice with DIO had impaired proliferative responses compared with lean controls. However, following OVA sensitization and challenge, splenocyte proliferation, interleukin (IL)-2 production and mast cell numbers were increased, whereas OVA-specific IgG\textsubscript{1} and IgE were decreased, in mice with DIO. Preliminary data from ob/ob mice indicate that airway responsiveness to intravenous methacholine is enhanced following OVA sensitization and challenge [32]. Dietary constituents might also have a role. For example, in mice fed diets supplemented with cholesterol, allergen sensitization and challenge resulted in increased numbers of bronchoalveolar lavage eosinophils and lymphocytes, and increased levels of IL-5 compared with chow-fed controls [33].

**Mechanistic basis for the relationship between obesity and asthma**

The data described above strongly support a relationship between obesity and asthma in which obesity antedates asthma. The basis for this relationship remains to be established, although several mechanisms have been proposed. These are summarized in Box 1 and are discussed below. The possibility also remains that the relationship between asthma and obesity is an epiphenomenon – that is, that obesity is a stand-in for some other causative factor. Physical activity does not appear to account for the relationship because several of the prospective studies which analyzed asthma incidence with increasing BMI found that adjusting for physical activity did not change the odds ratio [5,6**,11]. Differences in intake of specific dietary constituents could also contribute but have not yet been examined.

**Co-morbidities**

It is conceivable that obesity leads to asthma not directly but through its role in other disease processes. For example, obesity increases the risk of both GERD and SDB, and both conditions increase the risk of asthma. However, two recent epidemiological surveys demonstrated that the relationship between obesity and incident asthma was unaffected by adjustment for GERD or SDB [34**,35]. An important gap in our knowledge of the role of co-morbidities is the lack of data about the association between asthma and type 2 diabetes. Rana et al. [36] reported that asthma does not increase the risk of new-onset type 2 diabetes, but data addressing the opposite direction of causality do not exist. Because much is known about the relationship between obesity and insulin resistance, evidence of a relationship between asthma and type 2 diabetes might lead to a better understanding of the role of obesity in asthma, and could result in novel uses for already existing therapeutics to treat this susceptible population.

**Box 1 Proposed mechanisms for the relationship between obesity and asthma.**

**Common etiologies:** fetal programming, genetic pleiotropy

**Co-morbidities:** GERD, SDB, type 2 diabetes

**Effects of obesity on lung mechanics:** low FRC, reduced tidal volume

**Adipokines:** TNF-\(\alpha\), leptin, adiponectin
Common etiologies
The relationship between obesity and asthma could also be the result of fetal programming [37]. Low birth weight is associated with relatively increased body fat later in life [38]. Low–normal gestational age increases the risk for asthma at six years of age [39], and impaired fetal growth is also a risk factor for adult asthma [40]. Common genetic risk factors might also play a role in the relationship between obesity and asthma [37]. For example, genome-wide scans for asthma have indicated consensus linkage regions on chromosomes 5q, 6p, 11q and 12q, and these regions contain some candidate genes for obesity, including the genes encoding the β2-adrenoceptor, tumor necrosis factor α (TNF-α) and the glucocorticoid receptor [37]. Indeed, using statistical methods, Hallstrand et al. [41] concluded that shared genetic risk factors contributed substantially to the covariation between obesity and asthma in a study of the prevalence of these conditions in a population of monozygotic and dizygotic twins.

Low lung volume
Obese individuals breathe at a lower than normal functional residual capacity (FRC) [42–44] and the retractive effects of the lung parenchyma on the airways decline at low lung volume, leading to reduced airway caliber and increased airway responsiveness [45]. Obese humans also breathe with smaller tidal volumes and higher frequencies than lean humans [44]. This altered breathing pattern could be expected to promote airway narrowing because tidal straining of airway smooth muscle is a potent bronchodilator [46]. Because tidal straining also reduces the elastance of the airway wall, making the airways easier to strain with each cycle, breathing chronically with low tidal volumes at low FRC could lead to greater reductions in airway caliber than would be expected on the basis of changes in lung recoil alone. Two recent studies [42,43] concluded that the reduction in FRC that occurs in the obese accounts for only a fraction of the changes in specific airway conductance observed in these subjects. Similarly, Gold et al. [23] found no evidence that the effect of BMI on asthma could be explained by an abnormality in airway function related simply to reduced lung volumes. Factors other than differences in absolute lung volume or breathing pattern must be important in the AHR observed in obese mice because these measurements were made with the mice open-chested at a fixed positive end expiratory pressure and a fixed tidal volume that did not differ between strains [28,29].

Adipokines
The term ‘adipokine’ refers to proteins synthesized by and secreted from adipose tissue. These include cytokines, chemokines, hormones involved in energy regulation, as well as other factors. A partial list is presented in Table 1. In some cases, macrophages that infiltrate obese adipose tissue appear to be the source of these adipokines [47]. In both human and murine obesity, there are changes in the serum concentrations of many adipokines, and these changes could affect airway function, leading to asthma. For example, TNF-α is elevated in the serum of obese humans and obese mice, probably as result of increased production in adipose tissue macrophages. TNF-α has the capacity to induce AHR, so increased serum TNF-α in the obese could be acting to promote asthma (as discussed by Shore and Johnston [3]). In support of this hypothesis, obese mice genetically deficient in TNF-α do not develop other obesity-related diseases such as insulin resistance, whereas wild-type obese mice do [48]. Recent data indicate that adipose tissue is also a source of eotaxin, and that serum eotaxin is increased in obesity and declines with weight loss [49]. Eotaxin is a potent chemotactic factor for eosinophils and could contribute to asthma by promoting allergic inflammation in the lung. The complement protein C3α has also been shown to be capable of inducing AHR in mice [50]. Adipose tissue constitutively secretes both C3 and the other complement factors necessary to convert it into this alternatively activated form [51]. Visfatin is a recently identified adipokine produced from visceral fat that has been shown to mimic the effects of insulin [52]. Previously described as pre-B-cell colony-enhancing factor (PBEF), visfatin has recently been shown to enhance survival of vascular smooth muscle and to promote its maturation from a synthetic to a contractile phenotype [53]. If visfatin has similar effects in airway smooth muscle, then the increased serum concentrations of visfatin observed in obesity [52] could lead to AHR.

Table 1

<table>
<thead>
<tr>
<th>Adipokines</th>
<th>Cytokines</th>
<th>Chemokines</th>
<th>Hormones</th>
<th>Other factors</th>
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<td>TNF-α</td>
<td>IL-6</td>
<td>MCP-1</td>
<td>Leptin</td>
<td>PAI-1</td>
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<tr>
<td>IL-1</td>
<td>MIP-1α</td>
<td>Eotaxin</td>
<td>Adiponeclin</td>
<td>Angiotensinogen</td>
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<td>IL-6</td>
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<td></td>
<td>Resistin</td>
<td>Complement B, C3 and D</td>
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<td>Visfatin (PBEF)</td>
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<td>VEGF</td>
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<td>IL-10</td>
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<td>IL-1RA</td>
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IL-1RA, interleukin 1 receptor antagonist; MCP-1, monocyte chemotactic protein 1; MIP-1α, macrophage inflammatory protein 1α; PAI-1, plasminogen activator inhibitor 1; VEGF, vascular endothelial growth factor.
Serum leptin is markedly increased in the obese. Interestingly, even after correction for BMI, leptin is increased in the serum of asthmatic versus non-asthmatic children [54,55]. Allergic responses in the airways also increase serum leptin in mice [56**], indicating that events in the lung can modify adipose tissue. Leptin is a member of the IL-6 family of cytokines and has proinflammatory effects [57], suggesting that leptin could be contributing to the increased incidence of asthma observed in the obese. Data from mice provide some support for this hypothesis. OVA-sensitized mice treated with exogenous leptin develop greater AHR and greater IgE production following OVA aerosol challenge than do mice treated with saline [56**]. Leptin also augments pulmonary cytokine and chemokine expression induced by O3 exposure in mice [28]. These results are the first to demonstrate proinflammatory effects of leptin in the lung. Nevertheless, factors other than changes in leptin must be important for the innate AHR and the increased responses to O3 that are observed in obese mice [28,29**,30] because such changes are observed even in ob/ob mice that are genetically deficient in leptin [28].

Adiponectin is an insulin-sensitizing hormone that declines in obesity [58]. Adiponectin also has anti-inflammatory properties [59], so it is conceivable that obesity-related reductions in adiponectin contribute to the increased asthma observed in the obese. Preliminary data from our laboratory showing a reduction in OVA-induced airway inflammation and AHR in mice treated with exogenous adiponectin support this hypothesis (Shore et al., unpublished). Importantly, adiponectin inhibits proliferation of cultured vascular smooth muscle cells [60]. If adiponectin has similar effects on airway smooth muscle, declines in adiponectin in the obese could also be contributing to the increased smooth muscle mass that is a consistent feature of asthmatic airways.

Conclusions
Epidemiological data, studies of the effects of weight reduction and observations from obese mice all suggest a causal link between obesity and asthma. There are several biologically plausible mechanisms that could explain this relationship but much work still needs to be done to differentiate between them. It is increasingly clear that treatment of the obese asthmatic should include a weight loss program. Further understanding of the mechanistic basis for the relationship between obesity and asthma could lead to additional therapeutic strategies for treatment in this susceptible population.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


These authors report that asthma severity increases with BMI in women, particularly women with early menarche, but not in men.


This study demonstrated a relationship between obesity and asthma, but not obesity and allergic rhinitis, in a population of over one million Swedish male military conscripts, and shows that this relationship has remained unchanged for over three decades.

20. Kronander UN, Falkenberg M, Zetterstrom O: This study demonstrated a relationship between obesity and asthma, but not obesity and allergic rhinitis, in a population of over one million Swedish male military conscripts, and shows that this relationship has remained unchanged for over three decades.


22. Hakala K, Stenius-Aarniala B, Sovijarvi A: This study demonstrated a relationship between obesity and asthma, but not obesity and allergic rhinitis, in a population of over one million Swedish male military conscripts, and shows that this relationship has remained unchanged for over three decades.


The authors studied 1001 monozygotic and 383 dizygotic same-sex twin pairs from the University of Washington Twin Registry and used statistical methods to determine whether a shared genetic cause is responsible for the association between asthma and obesity.


This was the first study to demonstrate an increase in serum eotaxin in obese individuals.

   The authors describe expression of visfatin in visceral adipose tissue and insulin mimetic properties of visfatin. Visfatin was previously identified as PBEF, a cytokine produced by lymphocytes.
   The authors demonstrated release of leptin during allergic challenge and showed that exogenous leptin augments certain aspects of the allergic airway response in mice.