

## An Official American Thoracic Society Workshop Report: Obesity and Asthma

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**Rationale:** The developed world is currently facing an epidemic of obesity. With the increased prevalence of obesity has come the recognition that obesity is a risk factor for asthma.

**Objectives:** The purpose of this workshop was to bring together experts in the field of asthma, with experts in the field of obesity to review the current state-of-the-art knowledge regarding obesity and asthma, with the goal of furthering our understanding of the link between these two disease entities to help define important future directions for research.

**Methods:** Speakers were invited to give presentations highlighting recent developments in their area of expertise that were related to obesity and lung disease. These presentations were followed by interactive discussion. A writing committee from among the participants produced a document summarizing the proceedings.

**Measurements and Main Results:** The participants found that obesity was a risk factor for asthma in all demographic groups studied. Asthma in the obese may represent a unique phenotype of asthma, with more severe disease that does not respond as well to conventional therapy. Factors that could contribute to the pathogenesis of asthma in the obese include both mechanical factors and

altered inflammation and immune responses related to the obese state.

**Conclusions:** There is an urgent need for research to better understand the mechanisms of asthma in the obese, and to develop new therapies specifically targeted to this unique patient population.

**Keywords:** asthma; obesity; epidemiology; lung function

### EXECUTIVE SUMMARY

Obesity has recently been identified as a major risk factor for the development of asthma. Asthma in obese individuals tends to be more severe, does not respond as well to treatment, and is becoming a major public health issue in many countries. Research in this field is complicated by the need to bring together expertise from two fields that traditionally have little interaction: obesity/metabolism and asthma. The American Thoracic Society convened a symposium in May 2008, bringing together experts in the fields of both asthma and obesity to review our understanding of the relationship between these two syndromes, with the goals of identifying future research directions and ultimately to develop new strategies to intervene in obese individuals with asthma.

The first part of the conference reviewed the current state-of-the-art knowledge linking obesity and asthma: this included a review of the epidemiology linking asthma and obesity, data from animal models linking asthma and obesity, and our current understanding of the pathogenesis of asthma in the obese from genetic studies, physiology, and human studies.

A number of inflammatory mediators relevant to the innate and adaptive immune system are affected in obesity, and the relevance of these to asthma was reviewed in detail. Other factors, such as diet and macronutrient intake that are present in the Western diet, were also considered for the role they may have in contributing to inflammation in asthma and the pathogenesis of asthma in the obese.

Participants concluded that obesity was a major risk factor for asthma in all demographic groups studied. It likely represents a new phenotype of asthma. The mechanisms relating obesity and asthma are likely to include mechanical factors, inflammatory mediators, and immune responses that are all altered in the obese state. There is an urgent need to better understand the pathogenesis of asthma in the obese to develop new therapies to target this patient population.

### Background

The world is in the midst of an unprecedented obesity epidemic. With this epidemic has come a major shift in the type of diseases commonly encountered in medical practice, for example type 2

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diabetes (once a disease of the overweight elderly patient) is now a disease that may present in childhood. We are only just beginning to understand the impact obesity has on pulmonary health. This workshop was convened to review the current state-of-the-art understanding of the impact of obesity on pulmonary health, particularly as it relates to asthma. The goal was to identify current gaps in our knowledge, and potential important areas for future research.

### Methodology

A group of researchers with expertise in the mechanisms of inflammation in obesity, and a group of researchers and clinicians with expertise in lung disease and obesity were invited to a workshop on obesity and asthma in May 2008. Participants were asked to present the current state of science in their particular field of expertise. The literature was assessed by electronic and manual searches, but no specific instructions on how to search the literature or regarding inclusion and exclusion criteria were given or used. Consensus on the current state of knowledge, and directions for future research, were reached by active discussion at the workshop. A writing committee summarized the findings of the workshop, and all invited participants were given the opportunity to view and comment on the report, which was then revised to ensure that it reflected the proceedings of the workshop.

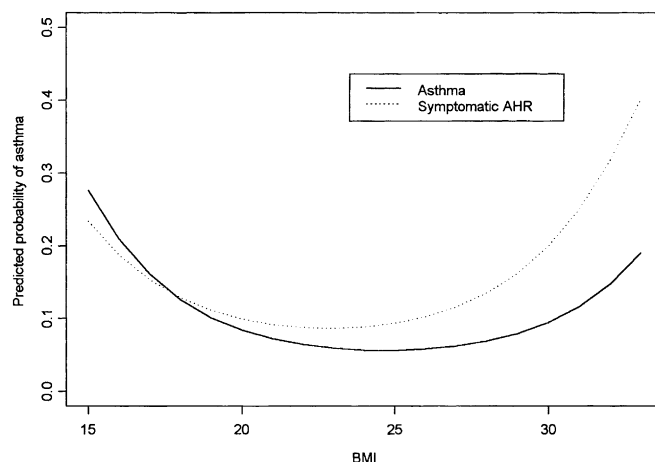
## EPIDEMIOLOGY OF ASTHMA AND OBESITY

### Cross-Sectional Epidemiologic Studies of Asthma and Obesity

There is an increased prevalence of asthma in the obese population. The majority of the forty cross-sectional studies published to date report a modest positive association between obesity and asthma, with odds ratios of 1.5 to 3.5 (1). Most of these studies are large, population-based investigations that use measured or reported body mass index (BMI) to quantify obesity, and self-reported physician diagnosis of asthma. It is important to note that some of these studies group underweight subjects (BMI < 18.5 kg/m<sup>2</sup>) and subjects of normal weight (BMI 18.5–24.9 kg/m<sup>2</sup>) together, but the prevalence of asthma increases at both extremes of BMI, giving the asthma–BMI curve a J shape (Figure 1) (2). If the increased prevalence of asthma in underweight populations is not accounted for, the magnitude of the obesity–asthma relationship may be underestimated. Though many of these studies are based on predominantly white populations (3–6), similar findings have been reported in Chinese (2) and Indian populations (7). Kim and Camargo specifically looked at the effect of race on the relationship between asthma and obesity in a U.S. population, and found that there was a positive relationship in both black and Hispanic men (8), suggesting that the relationship between asthma and obesity is consistent among diverse patient populations

### Prospective Epidemiologic Studies of Asthma and Obesity

There have been a number of studies of obesity and the risk of incident asthma, and all but one have shown a significant positive association between increasing obesity (usually BMI) and a new diagnosis of asthma, with modest risk ratios in the range of 1.1 to 3.5. However, among these studies there is heterogeneity in effect size and in the influence of sex on this relationship. These studies consistently show that obesity is a risk factor for obesity among women (9–13), though some report that obesity is not a risk factor among men (14–17). This may be related to differences in the number of males that are obese, giving limited power to some of these studies (15, 17), and different levels of obesity used in the obese category (14,



**Figure 1.** U-Shaped relationship between body mass index (kg/m<sup>2</sup>) and risk of asthma and symptomatic airway hyperresponsiveness in 3,386 men in Anqing, adjusting for age, intensity of cigarette smoking, skin test reactivity to one or more allergens, and familial correlations. Adapted with permission from Reference 2.

16). It may also reflect some diagnostic bias; Chinn and co-workers reported that obesity was a risk factor for asthma in women, whereas it was only a risk factor for wheeze (in the absence of cold symptoms) in men (18), suggesting that women with respiratory symptoms were more likely to be given a diagnosis of asthma than men. A recent meta-analysis of adult prospective studies reported that the odds of a new diagnosis of asthma at 1 year in overweight or obese versus normal-BMI individuals were significantly elevated at 1.51 (95% confidence interval [CI], 1.27–1.80), that there was a dose–response effect of increasing BMI leading to increasing odds of incident asthma, and that the effect of sex on this relationship was not significant (19). The authors estimated that 250,000 new adult cases of asthma each year in the United States may be attributable to overweight and obesity.

### Epidemiological Studies of Airway Hyperreactivity and Obesity

It is still unclear whether obesity increases the prevalence or incidence of airway hyperresponsiveness (AHR). Many cross-sectional studies have found no association between AHR and obesity in either children (20) (Table 1) or young adults (17, 21, 22). Other cross-sectional studies have found significant associations that are specific to sex. In 1,459 Taiwanese junior high school students, Huang and colleagues (23) found that girls in the lowest quintile of BMI had the lowest prevalence of AHR. However, there were no differences between the upper four quintiles, suggesting that this association was not driven by overweight and obesity, and there was no association between BMI and AHR in boys. In contrast, Chinn and coworkers, in a report of 11,277 adults from the European Community Respiratory Health Survey (aged 20–44 yr) (24) found an association between BMI and airway responsiveness that was significant in men, but not in women. The effect was small, in that a 10-unit increase in BMI would be needed to decrease PD<sub>20</sub>FEV<sub>1</sub> of one third of a doubling dose. There are few longitudinal studies to determine the effect of obesity on the incidence of AHR. In a case-control study of 61 men who developed AHR during a 4-year follow-up, and 244 control subjects, in the Greater Boston area (mean age 62 yr), Litonjua and colleagues (25) found that both low and high BMI at baseline were risk factors for the development of AHR.

However, Hancox and coworkers (17) found no association, in either men or women, between BMI and AHR in 1,000 subjects followed from age 9 to age 26 years. The reasons for these differing findings is unclear, but it is possible that the effect is small, and therefore only detectable in large studies, or is related to variation in demographics including age and degree of obesity, which may also be interrelated.

The combination of AHR and symptoms is used as a standard for defining asthma in epidemiologic studies (26), and several studies have shown that obesity is associated with the prevalence or incidence of asthma defined this way (2, 17, 27). Interestingly, in their longitudinal study, Hancox and colleagues (17) found that while obesity did not increase the risk of developing AHR, women were at increased risk of developing asthma symptoms, and at greater risk for the combination of symptoms and AHR. Similarly, Celedon and coworkers found that increasing BMI was associated with an increased risk of symptomatic AHR in a cross-sectional study of 7,109 Chinese adults (2). So, while increasing BMI may have a very small effect on the risk of AHR, increasing obesity is also likely to be associated with increasing symptoms, and the combination of increased symptoms and increased AHR would significantly increase the risk of an asthma diagnosis.

In studies of subjects with asthma, however, there is consistent evidence for a lack of association between BMI and AHR, indicating that the severity of AHR is not increased in obese individuals with asthma (28–32). This suggests that any effect of obesity on airway responsiveness has no further effect once the asthma phenotype is established. Indeed, Sood and colleagues came to just this conclusion following a study of 1,725 subjects referred for assessment of respiratory symptoms (33). They found that increasing BMI was associated with increasing airway responsiveness among subjects without AHR (without asthma), but was not associated with the severity of AHR in subjects with asthma.

### Limitations of the Epidemiologic Literature

Body mass index is a convenient and widely accepted measure of adiposity, but obesity is a heterogeneous disease, and BMI may not be the best measure of the effect of obesity on the lung. The mechanical effect of obesity on lung function is more strongly associated with central body fat distribution (34), and a subset of obese individuals demonstrate a phenotype of

enhanced systemic inflammation and insulin resistance (35) that may be more relevant in an inflammatory model of obesity–asthma pathogenesis.

Most large epidemiologic studies rely on self-reported weight and height, and self-reported physician's diagnosis of asthma. Concerns about misclassification of weight category and validity of asthma diagnosis have been raised. However, self-reported weight correlates strongly with measured weight in this population (36), and many of these studies used several definitions of asthma, with no change in results using different asthma definitions (10). In addition, a recent study suggests that the rate of false asthma diagnosis in those carrying a physician diagnosis of asthma is the same in the obese and nonobese: 32% of obese and 30% of nonobese subjects reporting asthma failed to meet more rigorous criteria for an asthma diagnosis (37). Thus, there is strong, consistent, and valid epidemiologic data to support a relationship between obesity and the development of asthma.

### ANIMALS MODELS SUPPORT A RELATIONSHIP BETWEEN OBESITY AND ASTHMA

Obese mice exhibit innate AHR. AHR is observed using both serotonin or methacholine as the bronchoconstricting agonist, similar to the nonspecific AHR that characterizes human asthma. This innate AHR has been observed regardless of the modality of obesity. For example, mice obese because of a genetic deficiency in the satiety hormone, leptin, or its receptor (*ob/ob* and *db/db* mice), because of a genetic deficiency in carboxypeptidase E, an enzyme involved in processing neuropeptides associated with satiety (*Cpe<sup>fat</sup>* mice), and mice rendered obese as the result of a high fat diet, each exhibit AHR compared with age- and sex-matched controls (38–41). The magnitude of this AHR appears to vary with the magnitude of the obesity. For example, *ob/ob* and *db/db* mice are the most obese of the models studied and also have the greatest degree of AHR (42). However, the duration of obesity may also play a role, since mice raised on high fat diets for 30 or more weeks exhibit AHR, whereas mice raised on this diet for only 16 weeks do not, even though the extent of their obesity is similar (41). Compared with lean mice, obese mice also have greater allergen-induced increases in airway responsiveness (43). Obese mice also have augmented pulmonary responses to acute ozone exposure, another asthma trigger. In particular, obese mice ex-

TABLE 1. STUDIES ON THE RELATIONSHIP BETWEEN AHR AND BMI

Study	Country	n	Approx. Age	Type of Study	Finding
Huang, 1999	Taiwan	1,459	"Junior High"	Cross-sectional	Relationship between AHR and BMI, girls only
Celedon, 2001	China	7,109	Mean = 37	Cross-sectional	Relationship between symptomatic AHR and BMI
Schachter, 2001	Australia	1,971	Mean = 35	Cross-sectional, pooled	No relationship AHR and BMI
Chinn, 2002	Europe, Australia, New Zealand, United States	11,277	20–44	Cross-sectional	Relationship between AHR and BMI, significant in men only
Litonjua, 2002	United States	61 with new-onset AHR 244 matched control subjects	Mean = 62 Mean = 61	Case control	New-onset AHR related to BMI
Schachter, 2003	Australia	5,933	7–12	Cross-sectional, pooled	No relationship AHR and BMI
Bustos, 2005	Chile	1,232	early	Cross-sectional	No relationship AHR and BMI
Hancox, 2005	New Zealand	~ 1,000	9–26	pooled data from birth cohort	No relationship AHR and BMI
Sood, 2006	United States	1,725	Adults	Cross-sectional, clinic referral population	Relationship between AHR, asthma, and BMI Relationship between AHR and BMI, only subjects without asthma

Definition of abbreviations: AHR, airway hyperresponsiveness; BMI, body mass index.

hibit greater ozone-induced increases in pulmonary resistance, airway responsiveness, and airway inflammation (38–41). It is unlikely that these changes are the result of obesity-related differences in the inhaled dose of ozone. Compared with lean individuals, obese humans also respond to ozone with greater increases in airway responsiveness and greater decrements in lung function (44, 45).

## **PATHOGENESIS OF ASTHMA IN THE OBESE**

### **Genetic Basis for the Obesity–Asthma Association**

Little is known about a potential genetic basis for the observed association between obesity and asthma. Hallstrand and colleagues reported an analysis of 1,001 monozygotic and 383 dizygotic same-sex American twin pairs, and found that 8% of the genetic component of obesity is shared with asthma, thus explaining the greatest amount of covariation in the association between the two diseases (46). In a subsequent large study of 29,183 Danish twin subjects, the age-adjusted genetic liabilities to obesity and asthma were significantly correlated only in women, with an *r* value of 0.28 (47). These results and the observed overlap in candidate genes and/or candidate genomic regions for obesity and asthma suggest that certain genetic variants may have pleiotropic effects on both obesity and asthma and/or influence pathways that are common to both diseases (e.g., growth).

Studies will be required to investigate whether specific genetic variants influence both obesity and asthma within the same population. Future genetic association studies will also have to account for potential epigenetic mechanisms, gene-by-gene interactions, and gene-by-environment interactions on obesity and asthma.

### **Obesity and Lung Function**

The most consistently reported effect of obesity on lung function is a decrease in the functional residual capacity (FRC) and expiratory reserve volume (ERV) (48, 49). The FRC is determined by the balance between inflationary and deflationary pressures on the lung. In the obese, increased deflationary pressures, due to increases in intra-abdominal pressure on the diaphragm and in fat mass on the chest wall (49), mean that the FRC occurs at a lower lung volume than in the nonobese individual (Figure 2). There are smaller effects on total lung capacity (TLC) that become more prominent in severe obesity (48, 49), but residual volume (RV) is usually well preserved (48, 50) or even elevated (51).

Airflow obstruction, as measured by the FEV<sub>1</sub>/FVC ratio, is not usually associated with obesity (52). Indeed, the FEV<sub>1</sub>/FVC ratio may be increased in obese individuals if airway closure and gas trapping reduces the FVC. As a consequence of breathing at lower FRC, airway caliber is decreased throughout the tidal breathing cycle, resulting in an increase in airway resistance (53). Some studies have suggested that the increase in airflow resistance may not be due entirely to the reduced lung volume (48, 54), but the cause of the additional resistance remains unknown.

It has been suggested that the mechanical effects of obesity on the lungs could alter airway smooth muscle (ASM) contractility and increase airway responsiveness (55). Breathing voluntarily at low lung volumes increases airway responsiveness to methacholine in lean subjects without asthma (56), an effect that is presumed to be a consequence of unloading of the airways due to the reduction in lung elastic recoil at low lung volumes. However, lung elastic recoil is increased in the obese (57), and may therefore offset the effects of low lung volumes.

Tidal volumes may be reduced in the obese (50), but this is not a consistent finding in obese subjects at rest (58, 59). Indeed, Boulet and coworkers (58) found that breathing patterns in obese and nonobese subjects were similar in the volume and frequency of both regular tidal breaths and occasional deep inspirations. However, in obese subjects breathing at low lung volumes, the airways remain at smaller caliber and the ASM is at shorter length throughout the breathing cycle. It is possible that this would change the contractile properties of the ASM, either by plastic adaptation to a shorter length (60) or alterations in cross-bridge cycling (61), resulting in an increase in ASM contractility and an increase in airway responsiveness.

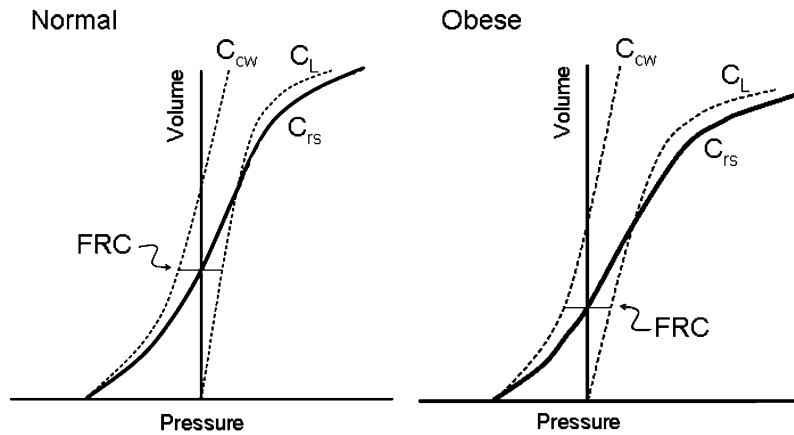
The effects of bronchoconstriction in obese individuals can be compounded by other mechanical changes that increase the sensation of dyspnea. Compared with nonobese individuals, bronchoconstriction in obese individuals causes greater hyperinflation (32, 59), possibly as a consequence of increased expiratory flow limitation (62, 63) and greater airway closure (64). Both expiratory flow limitation (65) and airway closure (66) contribute to changes in respiratory system reactance. In a recent study, obese and nonobese subjects without asthma had similar changes in FEV<sub>1</sub> following methacholine-induced airway narrowing, but the severity of dyspnea was greater in the obese group (59). This difference in symptoms was attributed to a greater change in respiratory system reactance in the obese, reflecting increased elastic loads. The occurrence of additional elastic loads in the obese during bronchoconstriction, which are not well reflected by spirometry, may explain why some obese individuals with asthma have more severe symptoms than their lean counterparts despite similar spirometry (67).

### **Obesity and Inflammation**

Obesity is associated with a state of chronic, low-grade inflammation that has been linked to conditions such as insulin resistance, type 2 diabetes, nonalcoholic fatty liver disease, and atherosclerosis. Both cellular mediators of immunity and proinflammatory signaling molecules are perturbed in obesity. The total leukocyte count correlates with the degree of obesity in otherwise healthy subjects (68), and the monocyte/macrophage and lymphocyte lineages, in particular, are altered in the obese state (69). In the obese, the number of adipose tissue resident macrophages is increased (Figure 3), and these macrophages secrete a large variety of inflammatory molecules such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), macrophage chemotactic protein-1 (MCP-1), and complement, and circulating plasma levels of these factors are increased in obesity (69). Adipocytes also produce a number of hormones, including leptin and adiponectin. Factors produced by adipose tissue and released into the circulation (adipokines) may affect the airway directly, or may act through cells of the immune system (Figure 4), as has been most clearly shown for leptin and adiponectin (70, 71). We will first address data linking adipokines to asthma and then consider the potential role that cells of the monocyte/macrophage lineage may play in obesity-associated asthma.

### **Role of Adipokines**

Leptin is a small, 16-kD protein secreted from adipocytes. Leptin was originally identified as a mediator of appetite and energy expenditure (72). Circulating plasma leptin levels are increased in proportion to obesity (73). Leptin's structure is similar to that of the IL-6 cytokine family, consisting of a four- $\alpha$ -helix bundle (74), and not surprisingly, leptin also has significant immunomodulatory functions. The action of leptin is mediated through a specific membrane receptor that has



**Figure 2.** Pressure–volume curves for the chest wall ( $C_{cw}$ ), lung ( $C_L$ ), and respiratory system ( $C_{rs}$ ) in normal-weight and obese individuals. In the obese individual there is a rightward shift in the chest wall curve, consistent with mass loading of the thorax, and a reduction the compliance of the lung and the respiratory system, resulting in a reduction in functional residual capacity (FRC).

homology to the IL-6 family of class 1 cytokine receptors (75). Several isoforms of this receptor have been identified that arise from alternative splicing and that differ in their signal transduction ability. The leptin receptor is expressed in the hypothalamus (where it regulates food intake and energy expenditure) (76), and also on all cell types of the innate and adaptive immune system (77–82). Leptin has multiple effects on cells of the innate immune system, such as promoting phagocytosis, proinflammatory cytokine production, chemotaxis, and surface markers of activation (80, 83–90). Leptin also affects cells of the adaptive immune response—in humans, leptin can induce proliferation of naïve T cells and modulate cytokine production toward production of Th1 cytokines (91). The importance of these effects of leptin on asthma are not known, though in rodent models of inflammatory bowel disease leptin appears to be a pivotal mediator: intestinal inflammation is decreased in leptin-deficient ob/ob mice (92), and T cells from leptin receptor-deficient (db/db) mice display reduced capacity to induce colitis (93). The role of leptin in pulmonary inflammation is not well defined, although leptin infusion increases allergen-induced airway hyperreactivity in normal-weight mice (70). Interestingly, this hyperresponsiveness occurs despite similar levels of airway inflammatory Th2 cytokine levels in leptin-infused versus saline-infused mice, suggesting that leptin may be producing effects on cells other than the Th2 lymphocyte population.

Another factor produced by adipose tissue that has been implicated in asthma is adiponectin (71). In contrast to leptin, adiponectin levels are decreased in obesity, diabetes, and atherosclerosis, and serum levels increase with weight loss (94, 95). In addition to important effects on fatty acid metabolism and insulin sensitivity, adiponectin also appears to have anti-inflammatory properties. Adiponectin infusion decreases allergen-induced airway hyperreactivity, but the mechanisms relating adiponectin to pulmonary disease are yet to be defined. Three species of adiponectin are recognized in serum: high molecular weight, hexameric, and trimeric (96, 97). T cadherin, which binds particularly to high-molecular-weight adiponectin, may be important for the actions of adiponectin in the lung as levels of adiponectin are markedly decreased in the BAL of T cadherin-deficient mice (whereas serum levels are increased) (98). Two other adiponectin receptors, Adipo R1 and R2, have also been identified (99). AdipoR1 is expressed in multiple cell types, including bronchial epithelium, but the role of Adipo R1 and R2 in the lung are not known.

### Human Studies of Adipokines and Asthma

A number of human studies have examined the relationship between leptin and/or adiponectin and asthma. Although the obesity–asthma association does not appear to be explained by either serum leptin or adiponectin alone (100, 101), both serum leptin and adiponectin concentrations do appear to be independently associated with asthma in population subgroups, even after adjusting for obesity (100–103).

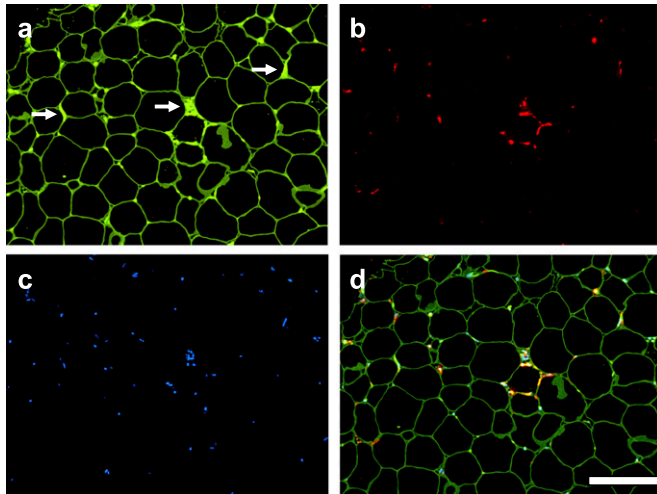
Most studies show a positive relationship between serum leptin and a negative association between serum adiponectin and the risk of asthma (100–103). These studies usually include asthma diagnosed on the basis of self report, parental report, or physician report (100–103). The only study that used a physiological phenotype of asthma (methacholine reactivity), in children did not show significant associations between serum leptin or adiponectin and asthma (104).

The strength of the associations described is usually modest. For leptin, the strength varies from odds ratios of about 2–4 for asthma (100, 102, 103), although odds ratios of about 6–13 have been described in a subgroup analyses in some studies (100, 102, 103). For adiponectin, odds ratio of about 0.5 for asthma have been described in the highest tertile of serum adiponectin concentration in premenopausal women (101).

The adipokine–asthma associations appear to be sex and age dependent. Associations are noted in prepubertal boys, peripubertal girls, and premenopausal women for leptin and peripubertal girls and premenopausal women for adiponectin (100–103). One longitudinal study reported that adiponectin (but not leptin) in term infants was associated with asthma (105). It is therefore possible that serum adipokines have different inflammatory effects in the perinatal period, as compared with later in life. Sex- and age-related factors may therefore modify the adipokine–asthma association.

Studies do not show a consistent relationship of adipokines with either atopic or nonatopic variants of asthma (100, 102, 103). One study showed a positive association between serum leptin and serum immunoglobulin E (103) and another showed a negative association between serum adiponectin and atopic dermatitis and eczema in children (102).

These cross-sectional studies are unable to determine causation or direction of the association between adipokines and asthma. In mice these relationships are bidirectional, with adipokines affecting allergen-induced airway hyperreactivity and asthma (allergen challenge) affecting adipokine production (70, 71). However, a small study of human subjects with mild asthma does not support the hypothesis established in mice that allergen inhalation affects serum leptin and adiponectin concentrations (106).



**Figure 3.** Adipose tissue is a complex tissue containing adipocytes (*a*, light green), vascular cells (*a*, bright green, arrows), and macrophages (*b*, red) among other stromal and immune cell populations. Local changes in adipokine production by adipocytes can affect leukocyte cytokine secretion and may influence both local and systemic inflammation. (*c*) DAPI counterstained nuclei. (*d*) Merged image. Scale bar = 200  $\mu$ m.

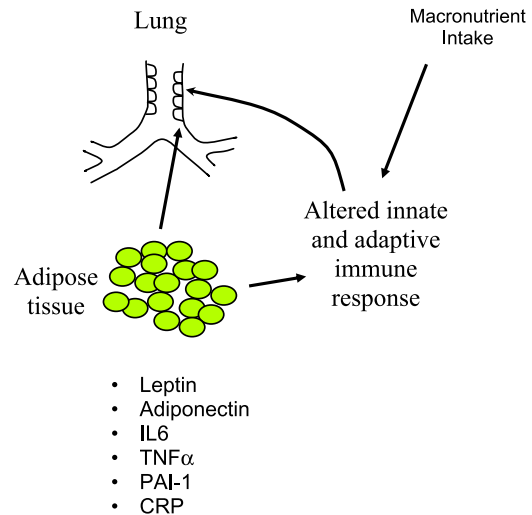
The human studies suggest that adipokines such as leptin and adiponectin may affect human asthma, though other factors such as age and sex may modify this affect. One cross-sectional study suggests that another adipokine, resistin, may reduce asthma risk in children (104). The role and mechanism of action of adipokines in asthma requires further study.

#### Role of Monocyte/Macrophage in Obesity-associated Inflammation

Cells of the monocyte/macrophage lineage are clearly altered in obesity. Studies in mice and humans show that over 800 genes associated with obesity are involved in inflammatory responses and macrophage activation, creating “a macrophage enhanced metabolic network” (107). Adipose tissue resident macrophages are increased in obesity (108) (Figure 3), and are an important source of proinflammatory cytokines in the obese. An active area of investigation is the study of macrophage populations in nonadipose tissues. For example, altered Kupfer cell function in the liver of obese individuals are involved in the pathogenesis of steatohepatitis (109). Alveolar macrophage function is likely also to be affected by obesity, as leptin (which is increased in obesity) can affect alveolar macrophage function. Leptin deficiency impairs alveolar macrophage function, and exogenous leptin can increase alveolar macrophage activation (110, 111). One of the important ways it may do this is through enhancing leukotriene production, as shown *in vitro* (112). This may be important clinically, as obese patients with asthma are relatively resistant to inhaled corticosteroids, but respond in a similar manner to antileukotrienes as do lean asthmatics (113).

#### Macronutrient Intake and Asthma

Another factor that may affect asthma in obese people is macronutrient intake. Both acute food ingestion and chronic overnutrition may exacerbate inflammation in the obese. Glucose loading causes an acute leukocytosis and evidence of increased reactive oxygen species in monocytes and neutrophils in the circulation (114). Similarly, a high-fat, high-carbohydrate



**Figure 4.** Factors that may be involved in the pathogenesis of asthma in the obese.

meal leads to increased markers of oxidative stress in mononuclear cells isolated from peripheral blood (115). This effect is exaggerated in obese compared with lean individuals. Conversely, fasting leads to a decrease in reactive oxygen species production from circulating neutrophils (116). The relevance of acute and chronic macronutrient intake in the pathophysiology of asthma is not known, but may represent a significant cause of oxidative stress in obese people. The role of macronutrients may be a useful area of future investigation, as oxidative stress is implicated in the pathophysiology of asthma (117). One study has already shown that alternate-day caloric restriction leads to decreased levels of reactive oxidant species in subjects with asthma, which is associated with significant improvements in peak flow and decreased asthma symptoms, although whether this was related to the caloric restriction or the weight loss is not known (118).

#### OBES ASTHMA: A NEW PHENOTYPE

Recent literature suggests that asthma is different in the obese than in the nonobese patient. Obesity not only affects lung mechanics, but has significant effects on asthma control and response to medication, and these changes appear to be independent of airway cellular inflammation. These differences may justify adding a new phenotype, “obesity-associated asthma,” to the existing list that includes allergic, occupational, exercise-induced, nocturnal, aspirin-sensitive, and severe asthma.

#### Obesity and Asthma Control

Obesity has a significant adverse effect on asthma control. Using data from the National Asthma Survey, a population-based study of asthma in four U.S. states, Taylor and colleagues showed that obese individuals with asthma had more severe symptoms and increased medication use in multivariate regression adjusted for age, sex, race, income, and education status (119). Vortmann and Eisner also found that obese subjects with asthma who were recruited following hospital discharge in Northern California had increased symptoms and decreased asthma-specific quality of life when controlling for age, sex, race, income, and educational status, but did not find

increased emergency health care utilization (120). In a cross-sectional survey study of health care plan participants in Colorado and the Northwestern United States, Mosen and coworkers showed that obesity has significant adverse effects on symptoms, medication use, and quality of life, and that, in addition, obese individuals with asthma have a 4.6-fold increased risk of hospitalization for asthma compared with nonobese individuals with asthma in multivariate analysis (121). The finding of increased hospitalizations in the obese by Mosen and colleagues contrasts with the finding of similar emergency health care utilization by Vortmann and Eisner. This may be related to the different patient populations; all participants in the study by Vortmann and Eisner had severe asthma and were recruited following a hospitalization for asthma, whereas Mosen and coworkers included individuals with asthma of all disease severities. Therefore, identifying strategies to improve asthma control in the obese should be a research priority in this field.

### Obesity and Airway Inflammation

Although obese individuals with asthma appear to have worse asthma control, the airways do not exhibit increased eosinophilic or neutrophilic inflammation (122, 123). In fact, two studies showed a negative correlation between either waist circumference or BMI, and sputum eosinophil count (28, 31). In addition, weight loss in obese individuals with asthma does not alter airway cellular inflammation, despite significant improvements in clinical measures of asthma (124). There is also no obvious cellular inflammation in the airways of unchallenged obese mice, and obese mice that are allergen sensitized and challenged also have *reduced* airway eosinophils compared with lean mice (43). The absence of *cellular* inflammation does not necessarily imply a lack of inflammation. Komakula and colleagues have reported that 8-isoprostane, a marker of oxidative stress, increases with increasing BMI in individuals with asthma (125), and oxidative stress is known to play a role in the pathophysiology of asthma. Future studies are required to identify the pathways that are responsible for asthma in the obese, so as to guide therapeutic intervention.

### Treatment of Asthma in the Obese

Obesity alters responses to asthma medications. Obese patients do not respond as well as normal-weight individuals to inhaled corticosteroids or inhaled corticosteroid/long-acting bronchodilator combination medications (113, 126), and have worsened asthma control with theophylline (127). A retrospective analysis using pooled data from participants in studies of asthma treatment (funded by Merck) found that obese individuals with asthma have attenuated response to inhaled corticosteroids, but obese and nonobese participants respond in a similar manner to leukotriene modifiers (113). Prospective studies are required to investigate these altered responses to medication. The explanation for this altered response to asthma controller therapy is likely to be more complicated than a difficulty with inhaled drug delivery or differences in airway mechanics, as illustrated by a recent study. Sutherland and coworkers reported that elevated BMI was associated with attenuated *in vitro* response to glucocorticoids in a well-characterized adult group of individuals with moderate to severe asthma (128). A better understanding of the pathogenesis of asthma in the obese is needed to improve therapies for this population.

An obvious therapeutic intervention that should be evaluated is weight loss. Many studies of surgical and diet-induced weight loss have shown that weight loss in the obese individual with asthma leads to significant improvements in asthma control

and lung function (as measured by FEV<sub>1</sub>, FVC, and peak flow) (118, 129–135), but this does not appear to correlate with any changes in airway eosinophilic or neutrophilic inflammation, and the effects on airway hyperreactivity are yet to be defined (124). Moreover, weight loss is one of the more difficult clinical interventions to successfully implement.

## CONCLUSIONS AND FUTURE DIRECTIONS

The writing committee summarized the main findings of the workshop and outlined major topics that should be the focus of future research studies.

### Epidemiology

Current knowledge:

- Obesity is significantly associated with both prevalent and incident asthma.
- Over-diagnosis of asthma is similar in obese and lean individuals.

Future directions:

- Define the natural history of asthma in the obese with longitudinal studies of well-characterized (in terms of both obesity and asthma) participants.
- Determine the effect of obesity and sex on incident and prevalent asthma at different developmental time points (*in utero*, early childhood, puberty, adult onset).
- Effect of obesity on previously diagnosed asthma compared with asthma developing in the setting of obesity.

### Pathogenesis

Current knowledge:

- The primary effect of obesity on lung function is a reduction in functional residual capacity and expiratory reserve volume. Obesity does not usually cause airway obstruction, and any effects on airway caliber are usually normalized after adjusting for lung volume.
- Obesity has little effect on the severity of airway hyperresponsiveness in subjects with asthma.
- Adipose tissue secretes a large number of proinflammatory cytokines and factors modulating immune function.
- Many factors produced by adipose tissue and dysregulated in obesity have been associated with asthma.
- Macronutrient intake may contribute to oxidative stress and systematic inflammation.

Future directions:

- Investigate the interaction between obesity and both genetic and epigenetic factors on asthma.
- Investigate the role of comorbidities of obesity, such as insulin resistance, sleep apnea, and gastroesophageal reflux, on the development of asthma in the obese.
- Determine the effect of obesity on airway development and structure/function relationships in the lung.
- Determine the effect of obesity on innate and adaptive immunity as it pertains to asthma.
- Understand the role of macronutrients and exercise on the development of asthma in the obese.

## Phenotype and Treatment Response in Asthma

### Current knowledge:

- Asthma severity appears to be increased in the obese.
- Response to controller therapy may be altered in obese individuals with asthma.

### Future directions:

- Prospective studies of the treatment of asthma in obese individuals with asthma, using multiple outcomes including control, physiology, oxidative stress, and airway inflammation.

This Workshop Report was prepared by an *ad hoc* subcommittee of the Assembly on Respiratory Structure and Function

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