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Obesity and Asthma

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Introduction

Over the last two decades, the convergence of secular trends indicating increases in the prevalence of both obesity and asthma has led to an hypothesis that these two disorders might be related. Data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES) indicate that 65 percent of U.S. adults ≥ 20 years of age are overweight or obese [41], a 10% increase when compared with the 1988-94 period [26]. Although asthma affects a smaller proportion of the U.S. population than does obesity, and while recent data suggest asthma prevalence may not be increasing as rapidly as in the past, the age-adjusted asthma prevalence of 7.9% reported based on 2005 National Health Interview Survey data [1] is more than twice that reported in 1984-1986 National Ambulatory Medical Care Survey data [48].

While the mechanisms underlying a putative relationship between obesity and asthma are not yet fully described, a relatively mature body of literature suggests that obesity increases the risk of incident asthma [12]. Obesity may also skew prevalent asthma towards a more difficult-to-control phenotype [23] and alter response to therapy [15,52]. Despite these emerging data, much remains to be elucidated [76], leading some to question whether the two disorders are related at all [78]. This review will address studies that could be interpreted to support the hypothesis that obesity leads to asthma, evaluating animal studies which provide biological underpinnings to an association between the two disorders, and clinical and epidemiologic studies which suggest the relationship between these two disorders is clinically important.

Obesity and Asthma Incidence and Prevalence

Cross-sectional and case-control studies in both children and adults have demonstrated an increased prevalence of asthma in obese individuals [8,17,19,32,47,54,60,64,79]. Representative of these studies is the example of Sin and colleagues, which utilized data from 16,692 participants (age ≥ 17 years) in the Third National Health and Nutrition Evaluation Survey (NHANES III). The investigators categorized body mass index (BMI, defined as kg/m^2) into quintiles and evaluated the relationship between BMI quintile and self-reported asthma, degree of airflow limitation and rescue bronchodilator use. In their analysis, individuals in the highest BMI quintile had the greatest odds of self-reported asthma, with an

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odds ratio (OR) of 1.50 [95% Confidence Interval (CI) 1.24 – 1.81]. Additionally, there was a trend for increasing odds of asthma as BMI increased (p = 0.001 for the trend), with similar findings of increased rescue bronchodilator use as BMI increased. These clinical outcomes were not associated with a similar trend towards increasing airflow limitation as BMI increased, however [64]. Another of these studies, reported by Beckett and colleagues, used data from 4,547 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study of 18-30 year-olds [8]. In this analysis, there was not an association between increasing baseline BMI quintile and baseline asthma prevalence (p = 0.74 for difference between quintiles), but elevated BMI at baseline was associated with an increased subsequent risk of developing asthma, with a hazard rate ratio [95% CI] of 1.6 [1.12-2.30] in the highest BMI quintile compared with the reference quintile.

Many of these cross-sectional and case-control studies benefit from the ability to evaluate large numbers of subjects and have provided important insights into the epidemiology of the two disorders. A potential limitation of studies of thousands of subjects is a limited capacity to carefully phenotype participants with regard to the exposure and outcome variables, and many of these studies relied on self-reported weight and height to determine BMI or self-reported asthma diagnosis to ascertain cases of asthma, raising the possibility of inaccuracies or biases related to reporting. This limitation does not apply to all epidemiologic studies of the obesity-asthma relationship, however, and in those that utilized measured rather than self-reported height and weight to define BMI [8,32,60], there was still a significant association between elevated BMI and asthma. Perhaps more limiting with regard to generalizability of many of these studies is the use of a self-reported physician's diagnosis of asthma, rather than formal physiologic evaluation, to determine cases, particularly because respiratory symptoms classified as asthma could be dyspnea due to obesity-related physiologic impairment rather than true asthma [11,13].

Prospective studies have often included more rigorous definitions of asthma in their study populations [16,20,27,33,44,51,53] and as a group introduce the additional benefit of being able to assess whether pre-existing obesity is associated with a subsequent increase in asthma risk. Most have shown a steady dose-response relationship with an elevation in incident asthma as BMI increases, and most demonstrate the effect to be stronger in women than men. Many of these longitudinal studies also control for diet and physical activity, strengthening the conclusion that it is obesity itself, and not a lack of exercise or a dietary factor, that is associated with asthma. As an example, Camargo and colleagues [16] performed a prospective analysis of the relationship between BMI and asthma in a study of 85,911 women followed for 4 years. In their multivariate model, the relative risk of incident asthma increased as BMI across six categories, with relative risks ranging between 0.9 (lowest BMI group) to 2.7 (highest BMI group, p for trend <0.001). This study differed from some other prospective studies in its enrollment of women only and the use of self-reported height and weight, but other prospective studies by Ford [27] and Nystad [51] and colleagues which included both men and women and based their definition of BMI on measured weight and height found associations between elevated BMI and incident asthma of similar strength.

Some of these prospective studies have suggested that the relationship between obesity and asthma is stronger in women, leading to the hypothesis that this effect may be modified by estrogen or other sex-based biologic difference. However, the difference in the point estimates of effect between men and women is usually small, and some studies have shown conflicting results. For example, in Chen and colleagues' 2002 Canadian National Population Health Survey study, the incidence of asthma was associated with the degree of baseline adiposity in women but not men [20], but two other prospective studies [33,43] demonstrated that the association between obesity and asthma was similar in men and women. In children, Castro-Rodríguez and colleagues showed that while there was no association between BMI and asthma

at age 6, the development of overweight or obesity between age 6 and 11 was associated with a seven-fold increased risk of new asthma symptoms, and the effect was strongest among females beginning puberty before age 11 [18]. Finally, in adult post-menopausal women, exogenous estrogen in the form of hormone replacement therapy has been associated with an increased risk of asthma [70], and a recent study showed that the association between BMI and asthma severity was stronger in women with early menarche than in women without early menarche [71]. While potential mechanisms underlying an association between sex hormones and asthma are being explored [35,36,42,56], the importance of these models in the obesity – asthma relationship in humans remains to be determined.

As noted, the majority of prospective studies have reported that obesity is a risk factor for the development of a new diagnosis of asthma, with risk or odds ratios of between 1.1 and 3.0 comparing the highest to lowest BMI categories, with the suggestion of a stronger effect in women. When this heterogeneity of effect was examined in a meta-analysis of studies investigating overweight and obesity as a risk factor for incident asthma, the authors concluded that, overall, overweight and obesity increased the odds of incident asthma in a dose-dependent manner, and that the strength of this relationship was similar in men and women. Random-effects meta-analysis of data from seven studies (n = 333,102) indicated that, compared with normal weight, overweight and obesity were associated with an increased odds of incident asthma, with an odds ratio of 1.51 [95% CI 1.27-1.80]. A dose-response effect of elevated BMI on asthma risk was observed; the OR for incident asthma comparing normal weight versus overweight (BMI 25 – 29.9) was 1.38 [1.17-1.62] versus 1.92 [1.43-2.59] comparing normal weight with obesity (BMI $\geq$ 30), with a $p < 0.0001$ for the trend. A similar increase in the odds of incident asthma due to overweight and obesity was observed in both men (1.46 [1.05-2.02]) and women (1.68 [1.45-1.94]) [12]. There are some studies, however, which call the strength of obesity as an asthma risk factor into question. For example, in the community-based cohort study of Hasler and colleagues which followed 591 adults between the ages of 20 and 40, asthma was significantly associated with obesity cross-sectionally (odds ratio 3.9 [1.2-12.2]), but a multivariate analysis revealed that obesity was not a risk factor for subsequent asthma; rather, asthma was a risk factor for subsequent obesity [38].

The pediatric literature also suggests a relationship between body mass and asthma risk, both with regard to asthma and atopy, a principal asthma risk factor in children. For example, in a prospective study of 9,828 children age 6 - 14 who they were able to follow for a median time of 5 years, Gold and colleagues reported that for girls, both higher BMI at entry and greater increase in BMI over the study were associated with a higher risk of asthma, with a 2.2 times greater risk of asthma in the highest versus lowest BMI quintile in girls. In both boys and girls enrolled in the study, greater increases in BMI over the course of the study were associated with an elevated risk of asthma [31]. A report from the Children's Health Study echoed the dose-dependence of increased BMI and asthma risk, with both overweight (BMI 25 – 29.9) and obesity (BMI $\geq$ 30) increasing the risk of incident asthma (risk ratios of 1.52 [1.14 – 2.03] and 1.60 [1.08 – 2.36], respectively), with obese boys having an increased risk of asthma compared to girls [29]. As in adults, not all studies of children show a significant association between obesity and asthma. Chinn and colleagues reported that in a group of British school children, the annualized odds of developing asthma was 1.09 [1.07 – 1.11] for both boys and girls, a number that did not change significantly when adjusting for BMI [22].

The relationship between obesity and atopy in children appears to be less robust than the relationship between obesity and asthma, as evidenced by data from pediatric participants in NHANES III. In unadjusted analyses, the prevalence of asthma and atopy increased with increasing BMI, but after adjusting for confounding factors, only the relationship between BMI and asthma remained significant (OR 1.77 [1.44 – 2.19]) [72]. In a study from Hancox and

colleagues, elevated BMI was modestly but significantly (OR 1.14 [1.10 – 1.30]) associated with positive skin tests and elevated IgE, a relationship not seen in boys [37].

Obesity and Asthma Severity

Compared with large-scale epidemiologic studies, there have been fewer reports of the effect of elevated body mass on biomarkers of asthma impairment and risk in well-characterized study populations. While studies have suggested that health status is impaired in obese individuals with asthma [73], it is not clear if this due to increased airway inflammation, altered pulmonary physiology or other variables that could influence health status. In children, a report from the Childhood Asthma Management Program suggested that there was not a statistically significant relationship between BMI and many markers of asthma control, including school absenteeism, emergency department care, requirement for corticosteroids or hospitalizations. Body mass index did not appear to affect eosinophil counts or IgE concentrations, and although there was a weak inverse relationship between BMI and bronchodilator reversibility ($\beta = -0.003$, $p = 0.02$), there was no impact of BMI on airway hyperresponsiveness to methacholine [66]. The generalizability of these data is somewhat limited, however, by the observation that most participants were pre-pubertal and that the median BMI was 17.09. A recent study by Santamaria and colleagues evaluated a population more obese (50 children with a BMI > 95th percentile) than that in CAMP, and while there was a high prevalence of atopy (58%) in the study population, significant differences were not found between lean and obese participants with regard to exhaled nitric oxide (FeNO) concentrations (a biomarker of airway inflammation) both independent of and adjusted for the diagnosis of atopy or asthma [57].

It is also not clear if obesity necessarily makes prevalent asthma severe, as there are conflicting data in this regard. The observation that obesity is associated with a more severe asthma phenotype has been supported in part by data from the TENOR study of severe asthmatics, in which the mean BMI in adults with severe asthma was 30.4 kg/m^2.[23] However, a recent report from the Severe Asthma Research Program (SARP) investigators [77] indicated that obesity was not more prevalent in severe [3] than in moderate asthma, raising some uncertainty about the importance of obesity as a modifier of asthma severity. This clinical controversy has perhaps been further underscored by recent studies which fail to demonstrate a robust relationship between obesity and biomarkers of airway inflammation in adult asthmatics. In an evaluation of lung function and spirometry in 297 asthmatics across the BMI spectrum, there was an inverse relationship between BMI and FeNO both in unadjusted analyses ($r_S = -0.307$, $p < 0.001$) and in analyses adjusted for age, FEV_1, sex, concurrent atopy and inhaled corticosteroid use [7]. McLachlan and colleagues reported similar findings in a population-based cohort of approximately 1,000 individuals, demonstrating that while adiposity (reflected in percentage of body fat) was associated with asthma and airflow limitation in women, there was not a meaningful association between FeNO or adiposity in women or men [49]. Finally, Todd and colleagues utilized induced sputum cell counts as an alternative means of assessing airway inflammation in 727 obese subjects with and without asthma. While sputum eosinophil counts were higher overall in subjects with asthma, there was not a significant correlation between BMI and sputum eosinophils either in asthmatic participants or in the study population as a whole [68]. While not conclusive, these data in aggregate do appear to suggest that biomarkers of airway inflammation do not necessarily increase as body mass increases in subjects with asthma.

Obesity and Pulmonary Physiology

Obesity has well-described effects on lung function, with physiologic studies suggesting that obesity has important mechanical effects that can lead to symptoms of dyspnea without necessarily causing the pathophysiologic changes commonly observed in asthma. Alterations

in airflows, respiratory system compliance, lung volumes, peripheral airway diameter and airway hyperresponsiveness have all been described in obesity.

Obesity causes airflow limitation, with reduction of both forced expiratory volume (FEV_1) and forced vital capacity (FVC) [14]. Unlike asthma, however, these reductions in airflows are typically symmetric and result in a preserved FEV_1/FVC ratio [64]. In fact, some authors have shown that the FEV_1/FVC ratio is increased in obesity, consistent with a restrictive physiology [14]. Reductions in absolute airflows are accompanied by a reduction in respiratory system compliance due to a combination of excess soft tissue weight compressing the thoracic cage, fatty infiltration of the chest wall, and increased pulmonary blood volume [6,24,50,80]. These alterations of pulmonary physiology lead obese individuals to breathe shallowly near their closing volume [40], which may be one cause of the observed subjective increase in dyspnea [64]. Lung volumes, particularly the expiratory reserve volume (ERV) and functional residual capacity (FRC) [9,14], are also reduced in obesity.

The reductions in lung volumes observed in obese individuals are associated with a reduction in peripheral airway diameter [55], a phenomenon which over time perturbs smooth muscle function, potentially increasing both airway obstruction and airway hyperresponsiveness (AHR) [28]. However, the available clinical data on obesity and AHR are conflicting. In the European Community Respiratory Health Survey, AHR increased with increasing BMI in men but not women [21], and in a case-control study from participants in the Normative Aging Study, high initial BMI was associated with the development of AHR to methacholine, with an odds ratio of 10 [2.6 – 37.9] when subjects in the highest BMI quintile were compared with those in the middle BMI quintile. There was also a linear relationship between increasing BMI over the study period and the subsequent development of AHR [46].

In contrast, Schachter and colleagues showed that in a group of 1,971 adults, BMI was associated with a diagnosis of asthma and symptoms of dyspnea and wheeze, but was not associated with either airflow obstruction or AHR [59]. Another study from this group, this time in almost 6,000 children, showed that elevated BMI was a risk factor for wheeze and cough, but not AHR or the diagnosis of asthma [58]. Thus, while it is apparent that obesity leads to a number of physiologic perturbations that could cause respiratory symptoms, physiologic studies do not uniformly support the conclusion that obesity leads increases in airway hyperresponsiveness.

Medical weight loss studies in asthmatics have demonstrated that weight loss can lead to improvements in both clinical and physiologic parameters. In an observational study of 14 obese patients with asthma before and after an eight week very-low-calorie diet, weight loss reduced diurnal peak flow variability, increased FRC, and improved measures of airflow limitation [34]. In a similarly-designed 6 month medical weight loss study of 58 obese women (24 of whom had asthma), weight loss improved lung function as measured by FEV_1 and FVC, but did not affect methacholine responsiveness [4]. Additionally, in an experimental study of two groups of 19 patients with obesity and asthma, the group randomized to supervised medical weight loss demonstrated improved lung function, asthma symptoms, and health status when compared with controls [65]. In a more substantial clinical weight-loss setting, studies of patients undergoing surgical weight-loss operations have demonstrated substantial improvements in physiologic parameters such as ERV and FRC, along with improvements in total lung capacity, residual volume [67] and even respiratory muscle function [75].

Systemic and Airway Inflammation in Obesity

In a subset of obese individuals, obesity is associated with a systemic proinflammatory state [25], which has been implicated in a number of the metabolic and cardiovascular complications of obesity. Whether this environment can lead to the development of airway inflammation and

asthma in humans is not yet known, but a number of observations suggest that obesity might impact the lung by modulating airway inflammation.

Much of the literature focusing on the relationship between obesity, airway inflammation and asthma has focused on the role of leptin. Leptin, the product of the *Ob* gene, is a central mediator of inflammation in obesity and has been shown to regulate T-cell proliferation and activation and recruit and activate monocytes and macrophages promote angiogenesis [63]. Leptin is also important for normal lung development, serving as a critical mediator of the differentiation of lipofibroblasts to normal fibroblasts and of pulmonary surfactant phospholipid synthesis [69].

Exogenous leptin has been shown to modulate allergic airway responses in mice, independent of obesity. Shore and colleagues sensitized and challenged lean BALB/cJ mice with ovalbumin and then infused either saline or leptin subcutaneously. Leptin infusion led to increased serum leptin levels and was associated with an enhancement of airway hyperresponsiveness and an increase in serum IgE following inhaled ovalbumin challenge, responses not observed in animals challenged with inhaled phosphate-buffered saline. There was no effect of leptin administration on bronchoalveolar lavage (BAL) fluid cell counts or lung tissue cytokine mRNA expression, however [62]. Endogenous leptin levels can be increased by overfeeding wild-type lean mice, leading to obesity and enhancing airway inflammatory response. Overfed mice which were subsequently sensitized and challenged with ovalbumin had higher antigen-induced T-cell responses, increased mitogen-induced splenocyte interferon-γ production, and increased number of tracheal mast cells compared to lean controls, although ovalbumin-specific immunoglobulin levels were paradoxically reduced in obese mice versus lean controls [5]. These studies suggest that leptin appears to have an important immunomodulatory role that is relevant to airway function and immune response, independent of body mass.

The relationship between obesity and enhanced airway inflammation cannot be attributed solely to leptin, however, as the obese leptin-deficient *ob/ob* mouse also demonstrates enhanced airway immune response. In a study of airway response to ozone, Shore and colleagues exposed both lean wild-type C57BL/6J mice and obese *ob/ob* mice to ozone, after which airway hyperresponsiveness (AHR) and airway inflammation were evaluated [61]. Exposed *ob*/*ob* mice had enhanced AHR when compared with lean controls, and while BAL levels of the CC chemokine eotaxin (an eosinophil chemoattractant) were increased, a predominantly Th1 inflammatory phenotypic response was observed in *ob*/*ob* mouse, with elevated BAL levels of IL-6 and the neutrophil chemoattractants MIP-2 and KC. In this same study, a subset of both lean and obese mice were given intraperitoneal injections of leptin prior to and directly after ozone exposure, and while leptin administration did not further enhance inflammatory responses in the *ob*/*ob* mice, leptin did significantly increase BAL levels of IL-6 and KC in lean control mice. This suggests that the mechanisms by which exogenous leptin alters airway immune response might vary between obese and lean animals, dependent on factors such as endogenous leptin concentrations, receptor number or affinity, or other concurrent modifications of inflammatory pathways.

A recent set of experiments from Johnston and colleagues evaluated AHR and other relevant biomarkers of airway inflammation following ovalbumin (OVA) sensitization and challenge in wild-type (lean) mice, *ob/ob* mice and *db/db* mice (deficient in the leptin receptor but with normal leptin concentrations). Innate AHR was increased in *ob/ob* mice when compared with wild-type mice, and ovalbumin sensitization and challenge further enhanced AHR in *ob/ob* mice and induced a nearly two-fold greater increase in serum IgE in *ob/ob* mice than that observed in wild-type mice. Although AHR and serum IgE were increased in the obese mice when compared with lean wild-type controls, commensurate increases in eosinophil counts and Th2 cytokine expression were not observed – in fact, paradoxically lower levels of these biomarkers were seen in the obese mice. The authors concluded that although allergic

sensitization increased pulmonary resistance and serum IgE, these alterations could not be attributed to the induction of a Th2 inflammatory profile in the airway [45].

Obesity as a modifier of therapeutic response in asthma

In obesity, systemic inflammation [25] may not only increase asthma risk but may also interfere with response to controller therapies, particularly inhaled corticosteroids. Many of the cytokines and other mediators found to be elevated in obesity-related systemic inflammation (such as leptin, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and C-reactive protein) have also been reported to mediate the development of glucocorticoid resistance in asthma [74]. Emerging clinical data suggest that there is potential for an interrelationship between obesity-related systemic inflammation and glucocorticoid resistance, in that TNF-α and IL-6 have been reported to be upregulated in lung macrophages from glucocorticoid-resistant asthmatics [39], suggesting that the cytokine environment described in obesity may modify therapeutic response to GCs. In this regard, two recent reports [15,52] indicate that overweight and obese patients with asthma may not respond as well as their lean counterparts to inhaled GCs, the most effective asthma controller therapy [2,30]. Peters-Golden and colleagues, in a *post hoc* analysis of clinical trials randomizing subjects to beclomethasone, montelukast or placebo, reported that clinical response to beclomethasone (as reflected by asthma control days, a composite of rescue beta-agonist use, nighttime awakenings and concurrent asthma exacerbation) was reduced as BMI increased, a trend not observed with montelukast. Significant difference with regard to lung function (measured as forced expiratory volume in one second, FEV_1 and rescue beta-agonist use were not demonstrated, however, and in all BMI strata there was a numerically-greater response to beclomethasone than to montelukast versus placebo, although these differences did not achieve statistical significance in overweight and obese participants [52]. A separate *post hoc* analysis by Boulet and Franssen also demonstrated a reduction in asthma control achieved in response to fluticasone as BMI increased; their pooled analysis of 1,242 asthmatic subjects allocated to either fluticasone, 100 mcg twice daily or fluticasone/salmeterol, 50 mcg/100 mcg twice daily suggested that, with both forms of asthma controller therapy, obese asthmatics were less likely to achieve asthma control than were those who were not obese [15].

Additionally, the elevations in TNF-α observed in obesity may be relevant to the treatment of obese asthmatics. A recent clinical trial demonstrated that increased expression of membrane-bound TNF-α, TNF-α receptor 1 and TNF-α converting enzyme in peripheral blood mononuclear cells from patients with severe asthma, were associated with GC insensitivity [3]. This study also suggested a beneficial effect of soluble TNF-α receptor etanercept in these patients, as shown by improvements in AHR, FEV_1 and asthma-related quality of life [10], raising the possibility that controller agents other than corticosteroids may be effective in obese asthmatics in whom systemic inflammation and GC insensitivity are shown to be important factors.

Conclusions

Although emerging data are beginning to shed light on the nature of the obesity-asthma relationship, much work remains to be done. Longitudinal epidemiologic investigations suggest that there is an association between the two disorders, with obesity increasing an individual's risk of developing asthma. In studies of carefully-phenotyped prevalent asthma, the impact of BMI on asthma status appears to be modest. Careful phenotyping studies in matched cohorts of subjects with and without both asthma and obesity are needed to describe how airway physiologic and inflammatory phenotypes are modified by obesity. Animal models have potential to expand our understanding, a continued emphasis on well-characterized animal models with regard to the interaction of obesity, environmental exposures (*e.g.* allergen,

infection), genetics, host factors (*e.g.* sex hormones) and airway inflammation are needed to guide further hypothesis development and testing in humans. Simultaneously, clinical investigators should conduct studies to identify the most appropriate interventions and outcomes with which to optimize care for this important subset of asthma patients.

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