Obesity and asthma

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Activity Objectives:

1. To understand the role that obesity plays as a risk factor for and disease modifier of asthma.
2. To identify the mechanisms involved in asthma pathogenesis.
3. To understand the evidence supporting lifestyle changes in influencing disease progression.
4. To identify the clinical characteristics of obese asthma in children and adults.

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Obesity is a vast public health problem and both a major risk factor and disease modifier for asthma in children and adults. Obese subjects have increased asthma risk, and obese asthmatic patients have more symptoms, more frequent and severe exacerbations, reduced response to several asthma medications, and decreased quality of life. Obese asthma is a complex syndrome, including different phenotypes of disease that are just beginning to be understood. We examine the epidemiology and characteristics of this syndrome in children and adults, as well as the changes in lung function seen in each age group. We then discuss the better recognized factors and mechanisms involved in disease pathogenesis, focusing particularly on diet and nutrients, the microbiome, inflammatory and metabolic dysregulation, and the genetics/genomics of obese asthma. Finally, we describe current evidence on the effect of weight loss and mention some important future directions for research in the field. (J Allergy Clin Immunol 2018;141:1169-79.)

Key words: *Asthma, obesity, obese asthma, metabolic syndrome, microbiome*

Obesity is both a major risk factor and a disease modifier of asthma in children and adults. Although obesity is defined according to a threshold body mass index (BMI), recent studies suggest that BMI *z* scores might be unreliable, particularly among children and adolescents with severe obesity.[1-3] In adults obesity is defined as a BMI of 30 kg/m^2 or greater, yet a given BMI might reflect vastly differing physiology and metabolic health. This distinction is likely important for asthma. Although serum IL-6 (produced by macrophages in adipose tissue and a marker of metabolic health) is a marker of asthma severity, some subjects with BMIs in the nonobese range have increased IL-6 levels[4]; Sideleva et al[5] found that adipose tissue inflammation is increased in obese patients with asthma compared with obese control

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Abbreviations used
AHR: Airway hyperresponsiveness
BMI: Body mass index
CAMP: Childhood Asthma Management Program
ERV: Expiratory reserve volume
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
ILC: Innate lymphoid cell
NO: Nitric oxide
RCT: Randomized controlled trial
SCFA: Short-chain fatty acid
SNP: Single nucleotide polymorphism
TLC: Total lung capacity

subjects. Metabolic dysfunction is more important than fat mass for asthma in obesity; however, most asthma studies have used BMI and metabolic dysfunction related to obesity synonymously. In this article we will report data on metabolic dysfunction, where available, but will otherwise use obesity as a marker of both fat mass and metabolic dysfunction.

EPIDEMIOLOGY OF OBESITY AND CHILDHOOD ASTHMA

Asthma affects approximately 6.5 million children (approximately 9% prevalence) in the United States.[6] Likewise, 17% of children in this country are obese, and another 15% are overweight.[7] Obesity is now recognized as a major risk factor for asthma: several longitudinal epidemiologic studies show that obesity or increased adiposity often precedes incident asthma.[8-16] Many studies have reported differing obesity-asthma associations by sex,[10,17-20] although results on which sex is more affected have been conflicting. Obesity is also associated with increased asthma severity.

Obesity-induced increases in asthma risk can start *in utero*. In a meta-analysis of more than 108,000 participants, we found that maternal obesity and weight gain during pregnancy are independently associated with approximately 15% to 30% increased risk of asthma in the offspring, and others have reported very similar findings.[21,22] This risk is not merely mediated by the child's own obesity.[23] Mechanisms involved can include inflammatory or other changes during pregnancy or early postnatal life,[24-26] and these mechanisms might explain why excessive weight gain in infancy has also been linked to recurrent wheezing and asthma.[27,28]

EPIDEMIOLOGY OF OBESITY AND ASTHMA IN ADULTS

A meta-analysis of several prospective studies involving more than 300,000 adults found a dose-response relationship between obesity and asthma: the odds ratio of incident asthma was 1.5 in the overweight and 1.9 in the obese groups compared with the lean group; in effect, 250,000 new asthma cases per year in the United States are related to obesity.[29] This relationship has radically changed the demographics of asthma in the United States: the prevalence of asthma in lean adults is 7.1%, and that in obese adults is 11.1%. The relationship is more striking in women; the prevalence of asthma in lean versus obese women is 7.9% and 14.6%, respectively.[30]

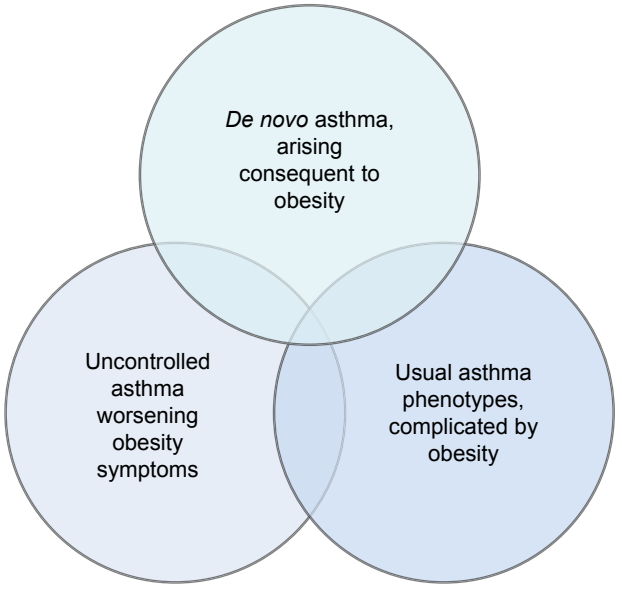

FIG 1. Obese asthma syndrome. The syndrome of obese asthma likely includes many phenotypes: those typically seen in lean subjects, now complicated by obesity; disease newly arising in obese subjects; and perhaps a separate phenotype characterized by increased response to environmental pollutants. Much work remains to be done to understand whether these are unique phenotypes that require individualized therapeutic approaches.

CLINICAL CHARACTERISTICS OF OBESE ASTHMA IN CHILDREN

On occasion, asthma can predispose to obesity,[31] obesity can confound its diagnosis,[32,33] or both can simply co-occur. However, the majority of observational and experimental evidence points to an "obese asthma" phenotype in which obesity modifies asthma.[34,35]

Obese children tend to have increased asthma severity,[36-38] poorer disease control,[39] and lower quality of life.[40] Many obese children with asthma tend to have T_H1-skewed responses, particularly in response to inflammatory stimuli, with at least part of these responses mediated by systemic inflammation, insulin resistance, and/or alterations in lipid metabolism.[41-43] These children and adolescents also tend to have a decreased response to asthma medications. Using data from the Childhood Asthma Management Program (CAMP), we described that overweight and obese children with asthma had a reduced response to inhaled corticosteroids (ICSs), leading to increased prednisone courses and moderate-to-severe exacerbations.[44] More recently, McGarry et al[45] reported that obese black and Latino adolescents were 24% more likely to be bronchodilator unresponsive than their nonobese peers. Moreover, among children hospitalized for asthma, obesity is associated with longer length of stay and higher risk of mechanical ventilation.[37] Obese children with asthma might also be more susceptible to having increased symptoms with exposure to indoor pollutants.[46]

CLINICAL CHARACTERISTICS OF OBESE ASTHMA IN ADULTS

Much like children, obese adults tend to have more severe asthma than lean adults, with a 4- to 6-fold higher risk of being hospitalized compared with lean adults with asthma.[47] Nearly 60% of adults with severe asthma in the United States are obese.[48] Obese patients also have worse asthma control and lower quality of life.[49] Obese asthmatic patients do not respond as well to standard controller