The effect of obesity, weight gain, and weight loss on asthma inception and control

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Purpose of review
There is ample and growing evidence that obesity increases the risk of asthma and morbidity from asthma. Here, we review recent clinical evidence supporting a causal link between obesity and asthma, and the mechanisms that may lead to 'obese asthma'.

Recent findings
Although in some children obesity and asthma simply co-occur, those with 'obese asthma' have increased asthma severity, lower quality of life, and reduced medication response. Underlying mechanistic pathways may include anatomical changes of the airways such as obstruction and dysanapsis, systemic inflammation, production of adipokines, impaired glucose–insulin metabolism, altered nutrient levels, genetic and epigenetic changes, and alterations in the airway and/or gut microbiome. A few small studies have shown that weight loss interventions may lead to improvements in asthma outcomes, but thus far research on therapeutic interventions for these children has been limited.

Summary
Obesity increases the risk of asthma – and worsens asthma severity or control – via multiple mechanisms. 'Obese asthma' is a complex, multifactorial phenotype in children. Obesity and its complications must be managed as part of the treatment of asthma in obese children.

Keywords
adipokines and asthma, airway dysanapsis, diet and asthma, insulin resistance, metabolic syndrome, microbiome and asthma, obese asthma, obesity-induced asthma

INTRODUCTION

Obesity is a well-known risk factor for cardiovascular disease and type-2 diabetes, and the processes that lead to these diseases may start in childhood and adolescence. Likewise, recent and growing evidence shows that childhood obesity affects the respiratory system. Obesity and its metabolic complications may affect lung function in otherwise healthy children, and increase the risk of new-onset asthma. This may start as early as *in utero* among children born to obese mothers. Among children with asthma, obesity is associated with increased symptoms and morbidity, decreased response to medications, and poorer quality of life. Here, we review recent evidence supporting a causal relation between obesity and asthma and the mechanisms that may underlie this link (see Fig. 1), as well as the importance of taking obesity into consideration when treating children with 'obese asthma'.

EPIDEMIOLOGY OF OBESITY AND ASTHMA

From 2001 to 2010, the prevalence of childhood asthma increased 1.4% per year in the United States, and currently over 6.3 million (~9%) children have asthma in this country [1]. Of these children, approximately 60% have persistent asthma, 58% have at least one exacerbation per year, and approximately 38.4% have uncontrolled symptoms [1].

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KEY POINTS

- Obesity increases the risk of incident asthma and asthma-related morbidity in children. 'Obese asthma' is a complex phenotype, and potential contributing mechanisms include abnormalities in airway and lung mechanics, airway and systemic inflammation, dietary and nutrient imbalances, changes in the gut and airway microbiome, and epigenetic changes.
- Large clinical studies are needed to assess whether weight loss leads to significant improvements in asthma severity or control, and whether pharmacological treatment of obesity and its complications plays a role in asthma management in these patients.

Obesity affects 12.7 million (17%) children and adolescents in the United States (with another 15% being overweight) [2]. Like childhood asthma, obesity disproportionately affects racial/ethnic minorities and those from lower socioeconomic status: up to 20–22% of Hispanics and non-Hispanic blacks are obese, compared with 14% of non-Hispanic whites. Moreover, obesity affects approximately 20% of children whose adult head of household did not finish high school, compared with approximately10% of children whose head of household completed college [2]. Childhood overweight and obesity constitute modifiable risk factors for cardiovascular disease, insulin resistance, diabetes, gastro-esophageal reflux disease (GERD), obstructive sleep apnea (OSA), and fatty liver disease. Since 2015, the Centers for Disease Control and Prevention (CDC) has also listed obesity as a major risk factor for childhood asthma.

'OBESE ASTHMA' IN CHILDHOOD

There is solid epidemiological evidence to support obesity as a risk factor for incident asthma [3▪▪,4,5▪▪]. Although obesity and asthma may simply co-occur in some children, growing evidence points toward the existence of an 'obese asthma' phenotype in childhood [6,7▪], in which obesity affects and modifies the asthma phenotype. This phenotype is likely to be complex and multifactorial, and our understanding of its subjacent causes and characteristics is far from complete.

Among children with asthma, obesity leads to increased symptoms, worse control [8], more frequent and/or severe exacerbations [9–12], decreased response to inhaled corticosteroids (ICSs) [13▪], and lower quality of life [14]. In a recent analysis of over 100 000 hospitalizations for asthma, obesity was associated with higher odds of mechanical ventilation and longer length of stay [11]. Although many studies [15–18] have reported differing effects of obesity on asthma by sex, their results have been conflicting and thus further research is needed on this topic.

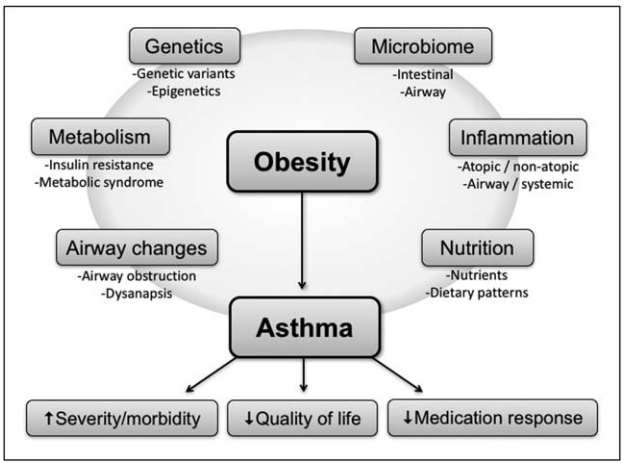


FIGURE 1. Multifactorial effects of obesity on childhood asthma. This figure depicts several mechanisms by which obesity affects asthma and asthma morbidity, with particular emphasis on pathways that have been the focus of research over the past 1–2 years, as described in this review.

MATERNAL OBESITY DURING PREGNANCY AND WEIGHT GAIN IN EARLY POSTNATAL LIFE

In a meta-analysis of 14 studies encompassing over 108 000 mother–child dyads, maternal obesity and maternal weight gain during pregnancy were associated with 21–31% and approximately 16% increased risk of asthma in the offspring [19], respectively. Similar findings were reported in a recent study [20▪] of almost 13 000 participants, with maternal prepregnancy overweight/obesity leading to 19–34% increased odds of childhood asthma. In this study [20▪], boys were more likely to have nonatopic asthma and girls more likely to have atopic asthma.

The increased risk of asthma conferred by maternal obesity or weight gain during pregnancy is beyond that of any indirect effect mediated by the child's own obesity [21], and may be explained by several mechanisms. Maternal obesity leads to changes in immune cell counts – including eosinophils and monocytes – the levels of inflammatory cytokines [i.e. interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, or interferon (IFN)-α2] [22▪,23], and lipid profiles in cord blood or early postnatal life [24]. Moreover, maternal obesity may lead to metabolic and oxidative alterations in the placenta and the fetus [25], and increased leptin level and insulin resistance in newborns [26]. Such

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pronounced changes may partly explain why excessive – or accelerated – weight gain in the first few months or years of life has also been linked to recurrent wheezing and incident asthma [27,28▪].

AIRWAY ANATOMY, MECHANICS, AND PHYSIOLOGY

A restrictive lung deficit – with decreased lung volumes, low forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), and a normal FEV_1/FVC ratio – has been reported in obese adults [29,30]. On the other hand, obese children have been shown to have a low-FEV_1/FVC ratio [3▪▪,31] consistently with an obstructive deficit that could partly account for their increased asthma morbidity. For example, a study [32▪] of over 2700 Taiwanese children showed that low FEV_1/FVC was the most significant 'mediator' between central obesity and active childhood asthma. Moreover, normal-weight children with asthma who become obese in early adulthood have further worsening of FEV_1/FVC (up to ~3% per each 10 kg/m^2 change in BMI), without significant changes in FVC [33].

Of interest, some obese children tend to have higher FVC and FEV_1 than their nonobese counterparts [34,35]. We recently reported that obesity is associated with airway dysanapsis (an incongruence in the growth of the lung parenchyma and the caliber of the airways that leads to larger lungs with flows that are normal but comparatively appear to be low) in several cohorts of children with and without asthma [36▪▪]. These children had normal/high FVC, normal FEV_1, and low FEV_1/FVC. Moreover, airway dysanapsis was associated with reduced response to albuterol or long-term ICS treatment in these children. This relative obstruction may thus be a 'developmental' feature instead of a marker of uncontrolled asthma, partly explaining why some obese asthmatic children have reduced response to bronchodilators [37▪] and ICS [13▪]. Overweight and obesity have also been correlated with lower maximal inspiratory pressures (MIPs) [38], further suggesting a complex compromise of pulmonary function in obese children. Future studies should help elucidate how these dysanaptic or obstructive defects in childhood and adolescence relate to the restrictive deficit found during adulthood.

INFLAMMATION

Whether obesity increases atopic inflammation is unclear, as some studies [39–41] report that obesity is associated with atopy but others report no association or an association with nonatopic asthma [42,43]. In a recent study using data from the National Health and Nutrition Examination Survey (NHANES), obesity was associated with asthma only among adolescents without eosinophilic airway inflammation. However, obesity was associated with increased disease among asthmatic children with eosinophilic airway inflammation [44▪]. These findings suggest that obesity predisposes to nonatopic asthma, while also increasing disease morbidity in children with atopic asthma (in whom obesity and atopy may have joint detrimental effects).

Beyond the airway, the systemic inflammatory milieu of obesity could also play an important role in asthma. Obese asthma may be related to Th1 rather than Th2 inflammatory profiles; such Th1 polarization has been associated with metabolic abnormalities, worse asthma severity and control, and abnormal lung function [45▪]. Different cytokines and adipokines associated with obesity may play a significant role, as evidenced by studies [42,46▪▪] linking higher leptin and/or lower adiponectin with worse asthma severity or control. Components of the innate immune system such as Th17 pathways and innate lymphoid cells have also been implicated [47,48▪▪]. Like other characteristics of obese asthma, its inflammatory profile is dynamic and may differ by sex and life stage. For example, a recent study [49▪] found evidence of more prominent macrophage activation among girls, with soluble CD163 (a marker of macrophage activation) associated with higher android fat deposition, lower FEV_1, and worse asthma control.

DIET AND NUTRIENTS

Dietary factors are evidently associated with childhood obesity, and several studies over the past few years have reported similar associations with asthma [50]. Breastfeeding [51,52] and the Mediterranean diet [53,54] have each been associated to lower risk of both obesity and asthma. We recently described that a diet abundant in sweets and dairy products is associated with increased asthma risk (and with higher serum IL-17F), whereas frequent consumption of vegetables and grains was linked to lower odds of asthma [55]. High-fat meals can lead to neutrophilic airway inflammation and decreased bronchodilator response among patients with asthma [56▪]. Among specific nutrients, low vitamin D could represent a common path for both obesity and asthma [57]. In a recent analysis, vitamin D deficiency was associated with low lung function among obese children with asthma, but not among those of normal weight [58▪]. Another recent study [59] reported that high BMI was associated with asthma exacerbations among children with low

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vitamin D, with cathelicidin (an innate immunity polypeptide found in macrophages and neutrophils) potentially playing a mediating role. Omega-3 and omega-6 fatty acids have also been linked to asthma [60], and fish oil supplementation in early life has been reported to modulate immune responses [61]. Research is lacking, however, on whether dietary modifications can prospectively reduce obesity-related asthma risk or morbidity.

INSULIN RESISTANCE AND THE METABOLIC SYNDROME

Insulin resistance and the metabolic syndrome have been associated with lower lung function in adolescents with and without asthma, with a more pronounced effect among those with asthma (up to 10% lower FEV_1/FVC than that of healthy adolescents) [62▪]. More recently, obesity was shown to be associated with airway hyper-responsiveness (AHR) in children with asthma and coexisting insulin resistance [63▪], but not in those with asthma but no insulin resistance. This could partly explain why some prior reports found no association between obesity and AHR. Several studies [64–66] have associated dyslipidemia with asthma, independently of – or in synergy with – obesity. Potential mechanisms for a causal effect of insulin resistance on asthma include Th1 polarization [45▪], increased allergic sensitization [67], increased oxidative stress [68], airway smooth muscle dysfunction and fibroblast proliferation [69,70], or airway epithelial damage, among others.

GENETICS AND GENOMICS

While obesity and asthma have significant hereditary components, results from studies looking at the genetic determinants of 'obese asthma' have been inauspicious. In a large study [71▪] of over 23 000 children, only *DENND1B* (DENN Domain Containing 1B) was associated with both BMI and asthma. Candidate-gene studies have reported associations or interactions between obesity and genes including *PRKCA* (protein kinase C alpha) [72] and *ADRB3* (adrenergic receptor beta-3) [73] on asthma. More recent approaches have yielded more promising results: a study looking at asthma genes selected from the literature reported effect size differences between asthma risk in normal-weight children vs. obese children. After stratifying the analysis by obesity, that study [74] replicated four potential asthma genes in normal-weight children, 17 in obese children, and five in both normal-weight and obese children. Moreover, a recent Mendelian randomization study [5▪▪] reported that a weighted allele score using 32 SNPs previously associated with BMI was also strongly associated asthma at approximately 7 years of age.

Obese asthma may also be caused by epigenetic mechanisms. A recent study [75] identified significant DNA methylation changes in peripheral blood mononuclear cells in children with obesity and asthma, and a study [76▪▪] in mice and humans reported that *CHI3L1* (chitinase 3-like 1) can be induced by a high-fat diet, and contributes to truncal obesity and asthma symptoms.

THE MICROBIOME

Exposure to antibiotics in early life has been associated with both asthma [77] and obesity [78]. Although confounding by respiratory infections may partly explain the estimated effect of antibiotics on asthma, the same is not true for the potential effects of antibiotic use on obesity. Alterations in the nasal or airway microbiome have been described in asthma [79]. Similarly, changes in the gut microbiome have been implicated in the pathogenesis of obesity [80] and atopic diseases (including asthma) [81,82▪▪]. Moreover, aberrant responses to these microbiota have been reported to precede asthma and allergy [83]. Probiotic supplementation has been shown to reduce the risk of atopy [84] but not asthma.

Our understanding of the importance of the microbiome in both obesity and asthma is still incipient, and several aspects – such as sampling-related variability [85] – need to be addressed. Nonetheless, obesity could plausibly induce or facilitate changes in the microbiome that lead to asthma. Alternatively, microbiome–host dysfunction may increase the risk of both obesity and asthma. Several factors associated with asthma, including living in an urban environment, diet, Caesarean delivery, or repeated antibiotic use, could be linked to the microbiome and – in some children – obesity. Future research in this field could yield preventive or therapeutic approaches for patients with obese asthma [86▪▪].

MISCLASSIFICATION

Researchers and clinicians must be aware that not all children with coexisting obesity and asthma have 'obese asthma'. Comorbidities such as OSA or GERD may cause difficulty breathing or chest pain/tightness [87,88], and obesity (and related deconditioning) may lead to dyspnea or exercise limitation [89,90]. Such symptoms can mimic asthma and lead to misdiagnosis or misattribution. Moreover, some children with severe asthma (or whose parents

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perceive it to be severe) may have reduced physical activity leading to obesity ('reverse causation') [91].

Much of the existing literature has used BMI to define obesity. Recent evidence suggests that, while convenient, BMI may not be the best measure to encapsulate the complexities of 'obese asthma' [16,92–95]. Most, but not all [96] of these studies have reported that other measures of adiposity type and distribution may increase our understanding of 'obese asthma' phenotypes (e.g. central vs. truncal obesity).

WEIGHT LOSS AND MANAGEMENT OF OBESITY COMPLICATIONS

In spite of growing awareness of 'obese asthma', this entity is not being appropriately recognized and managed. For example, a recent study [97] showed that less than 10% of obese children who had been hospitalized with asthma had an obesity discharge code or received treatment for their obesity.

Data are scarce on weight loss in children with asthma. In a pilot study [98] of 28 children, diet-induced weight loss in obese children with asthma was associated with improved asthma control and lower C-reactive protein (CRP). Similarly, in a non-controlled intervention study [99] of 20 children, diet-induced weight loss was associated with decreased exercise-induced bronchospasm. A recent randomized, controlled trial (RCT) in 87 children improved asthma outcomes for both the intervention (weight loss) and control groups, with some effects – such as asthma control and quality of life – being more pronounced in the intervention group [100▪]. In another RCT in 51 adolescents, a normo-caloric diet led to reductions in BMI that correlated with improved quality of life and reduced asthma exacerbations [101▪]. Although these results are promising and should prompt providers to consider managing obesity in children asthma, larger RCTs are needed to further elucidate the effects of weight loss on 'obese asthma' in children.

Beyond weight loss, few other therapeutic options have been explored in 'obese asthma'. A recent retrospective study [102] in adults found that the use of metformin among patients with diabetes and asthma was associated with improved asthma outcomes. Metformin, which acts via AMP-protein kinase (AMPK), has been shown to decrease eosinophilic airway inflammation and inhibit airway smooth muscle hypertrophy in murine models [103▪,104]. A recent meta-analysis showed a modest reduction in BMI from metformin use in nondiabetic obese adolescents [105], and another study [106▪] showed improved insulin profiles. Thus, metformin may represent a possible adjunct therapy in obese asthma that warrants further investigation. Finally, some studies in adults have suggested that, whereas response to ICS may be decreased, response to leukotriene antagonists may be preserved in obese patients with asthma [107].

CONCLUSION

Obesity increases the risk of incident asthma and worsens asthma severity or control via multiple mechanisms. Thus, obesity and its complications should be managed as part of the treatment of 'obese asthma' in children. Like both obesity and asthma, 'obese asthma' is a complex phenotype in children. Although our understanding of this phenotype has increased over the last few years, its underlying mechanistic pathways and appropriate management approach are far from fully elucidated and warrant further research.

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Conflicts of interest

There are no conflicts of interest.

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