The Challenge of Obesity and Asthma in Children and Adolescents

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ABSTRACT

Obesity and asthma each affect millions of people worldwide and the prevalence of both diseases has substantially risen in the last few decades. Solid epidemiological and experimental evidence strongly suggest that obesity increases asthma risk and severity, leading to growing recognition of an obese asthma phenotype. This phenotype is complex and multifactorial, differs between children and adults, and likely encompasses several sub-phenotypes. In this article, we will review the characteristics of obese asthma in children, as well as some of its underlying pathways. Furthermore, we will discuss some remaining challenges in the research, diagnosis, and management of obese asthma in children. (BRN Rev. 2018;4:70-83)

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INTRODUCTION

Obesity is a chief risk factor for the metabolic syndrome, cardiovascular disease, and diabetes. The processes that lead to these complications may start as early as in childhood. In the United States (U.S.), approximately 17% of children are obese (defined as a body mass index [BMI] ≥ 95th percentile for age and sex) and another 15% are overweight (BMI ≥ 85th percentile and < 95th percentile). In Catalonia, the prevalence of overweight and obesity is ~15% and ~20%, respectively, and tends to be higher among children with parents of low socio-economic status or lower education levels. While obesity is currently defined using BMI, recent studies have suggested that this definition may be unreliable and that metabolic dysfunction may be more important than adipose tissue mass.

Asthma affects ~9.5% of children in the U.S. and the prevalence of asthma can be as high as ~30% in other countries; in Spain, the prevalence of asthma has been reported as ranging from 9.5% to 16%. Based on several longitudinal epidemiological studies, obesity is now recognized as a risk factor for asthma and associated with worse asthma outcomes. However, it is not clear whether this association holds true for all children with obesity and asthma. In this review, we will first summarise our current understanding of obese asthma in children, and then discuss some of the challenges in the study and management of this phenotype.

THE OBESE ASTHMA PHENOTYPE

Among children and adults with asthma, obesity has been associated with worse asthma severity, more frequent exacerbations, poor asthma control, worse quality of life, longer hospital length of stay, and a higher risk of requiring intubation and mechanical ventilation. Obese children with asthma also seem to have a reduced response to asthma medications. Analysing data from the Childhood Asthma Management Program (CAMP), we reported that obese asthmatic children had a diminished response to inhaled corticosteroids (ICS) and that those participants had more frequent exacerbations and need for oral steroid courses for asthma. Obese asthmatic adolescents may also have reduced response to bronchodilators compared with non-obese adolescents with asthma. However, much like obesity and asthma, obese asthma (in both children and adults) is likely a complex phenotype with numerous contributing risk factors and underlying pathways.
and abnormal monocyte and dendritic cell responses. Placenta and newborn from obese women also show increased oxidative stress and higher triglyceride levels. More recently, Costa et al. reported gene expression changes in umbilical vein endothelium from infants born to overweight or obese mothers compared with those born from normal-weight women; pathway analysis suggested these changes were related to mitochondrial and lipid metabolism. These early-life alterations could also explain reports that rapid or excess weight gain as early as in infancy are associated with increased risk of wheezing.

**OBESITY AND LUNG FUNCTION**

Childhood obesity has significant effects on pulmonary function. In the 1990s and 2000s, investigators started reporting that higher weight or higher BMI were associated with increasing forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC), and with lower FEV₁/FVC ratios, in children with and without asthma. We recently reported an increased prevalence of airway dysanapsis in overweight and obese children with and without asthma. The term was coined to describe an incongruence between the growth of the diameter of the airways and
the volume of the lungs. Dysanapsis has been reported among breath-hold divers, who use techniques that hyperinflate their lungs in order to provide extra oxygen and pressure protection. In children from six independent cohorts, we found that obesity was associated with normal or supra-normal FEV₁ and FVC, with larger increases in FVC leading to a low FEV₁/FVC ratio. Among obese children with asthma, dysanapsis was also associated with higher asthma symptoms, morbidity, and medication use.

These findings are quite different from adults, in whom obesity has been associated with a restrictive deficit characterized by low lung volumes, symmetrically reduced FEV₁ and FVC, and a normal FEV₁/FVC ratio. In a recently published meta-analysis, we reported that age indeed modifies the association between obesity and spirometry results: in adults, overweight/obesity was associated with lower FEV₁ and FVC with a normal FEV₁/FVC ratio. Age (and likely disease onset or duration) are also important modifiers of the relation between obesity and lung function in subjects with asthma: Strunk et al. reported that, among participants in the CAMP who were not obese during the trial, those who became obese afterwards had significant decreases in FEV₁ and FEV₁/FVC ratio at ~26-30 years of age, compared with those who never became obese, with no significant changes in FVC.

Only a few studies in paediatrics have evaluated the effect of obesity on lung volumes, and most have reported reductions in functional residual capacity (FRC) and residual volume (RV), with little or no effect on total lung capacity (TLC). Thus, further research is needed in this area. Likewise, it is unclear whether excess weight leads to increased airway hyper-responsiveness (AHR) in children and further research is needed on the topic.

INFLAMMATION AND METABOLIC DYSFUNCTION

Many consequences and complications of obesity arise from its inflammatory milieu. Like adults, obese children are predisposed to insulin resistance and systemic inflammation. Thus, it has been proposed that asthma in the obese results from such systemic inflammatory state, rather than classical type 2 T helper (Th2) atopic airway inflammation. Several studies have reported that obese children with asthma tend to have increased type 1 T helper (Th1) responses and that some of those effects are mediated by metabolic dysregulation, particularly in more markedly obese adolescents. However, others have described that obesity is associated with higher risk of atopic sensitization in children and adults. Our group analysed data from adolescents who participated in the U.S. National Health and Nutrition Examination Survey (NHANES) and reported that high BMI was linked to asthma risk only among those without evidence of eosinophilic airway inflammation, as measured by exhaled nitric oxide (FeNO) (Fig. 2). Yet, in adolescents with asthma, being obese and having elevated FeNO synergistically worsened asthma control and severity. This suggests that both Th2 and non-Th2 inflammatory responses may play a role in obese asthma.

Adipose tissue, rather than an inert storage of energy reserves, is very active metabolically, producing adipokines and other inflammatory
cytokines that may affect the lungs and the immune system, including eosinophils, macrophages, and innate lymphoid cells (ILCs) (Fig. 3). Leptin is markedly increased in many obese subjects, and higher serum leptin levels have been associated with lower lung function in obese children and adolescents. Conversely, adiponectin has anti-inflammatory properties and is decreased in obesity, being associated with less exercise-induced bronchospasm in children with asthma, fewer exacerbations, and fewer symptoms. Changes in adipokine production and balance may alter eosinophil survival and migration to the lungs and may induce activation of macrophages to produce systemic and airway inflammation. Unfortunately, most studies to date have been cross-sectional, and we do not know whether these changes are causal (i.e. higher leptin or lower adiponectin have an effect on the lungs leading to increased asthma morbidity) or whether they simply act as biomarkers (i.e. the changes are not causal but may reflect the underlying changes at play).

Metabolic dysfunction may be more important in obese asthma than mere excess fat mass. Hyperglycaemia and the body’s attempt to compensate by elevating insulin levels may lead to airway epithelial damage and proliferation of airway smooth muscle, which in turn may worsen AHR and airway remodelling. We previously reported that insulin resistance and metabolic syndrome are associated with decreased spirometry in adolescents, and that this negative effect may be synergistic among adolescents with asthma. Insulin may also increase AHR by altering parasympathetic airway tone and regulation. IL-6 is elevated in obese subjects with metabolic dysregulation, and in adults it has been associated with increased asthma severity. Furthermore, IL-6...
trans-signalling increases airway smooth muscle expression of genes associated with immune responses, hypoxia, and airway remodelling.

**DIET AND NUTRIENTS**

Dietary factors are clearly linked to obesity and some of these dietary patterns have also been associated with asthma. A diet poor in grains and vegetables but rich in consumption of sweets and processed dairy products has also been associated with higher risk of asthma. Similarly, frequent intake of beverages with high sugar content has been linked to asthma. On the contrary, breastfeeding has been reported as a protective factor for both diseases, but the findings for asthma have been more inconsistent (perhaps partly due to variable accounting for introduction of foodstuff across

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**Figure 3.** Proposed role of adipokines linking obese adipose tissue and asthma. A) Adipokines can regulate eosinophil and macrophage activation and function. B) Adipokine changes may result in migration and accumulation of eosinophils in the lung tissue. C) Activated macrophages in obese adipose tissue may play an important role in systemic and airway inflammation (reprinted with permission from Kim SH et al.9).

AAM: alternatively-activated macrophages. AHR: airway hyper-reactivity; CAM: classically-activated macrophages; IL: interleukin; TNF-α: tumour necrosis factor alpha.
studies\textsuperscript{66,67}. Likewise, a Mediterranean diet, which is a protective risk factor against obesity and its metabolic complications, has been associated with lower risk of recurrent wheezing and asthma in children and adults\textsuperscript{68,69}.

With regard to specific nutrients, obese persons tend to have lower vitamin D levels\textsuperscript{70}, and low maternal vitamin D levels during pregnancy are associated with higher risk of obesity in their offspring\textsuperscript{71}. Conversely, vitamin D insufficiency has been associated with severe asthma exacerbations and worse asthma outcomes\textsuperscript{72-75}. Furthermore, a meta-analysis of two recent clinical trials showed that vitamin D supplementation during pregnancy leads to 25\% lower risk of asthma or recurrent wheezing in children up to three years of age; the strongest effect (~45\% reduction) was seen among children from women with sufficient levels (≥ 30 ng/ml) at the start of the trials\textsuperscript{76,77}. Intake of micronutrients such as vitamin E or zinc during pregnancy has also been linked to lower odds of asthma\textsuperscript{69}. Other nutrients that may be involved in obese asthma include Omega-3 and Omega-6 fatty acids, which have been associated with lower and higher risks of asthma, respectively\textsuperscript{78,79}. Beyond observational analyses, studies such as an ongoing randomized controlled trial (RCT) of Omega-3 fatty acids for obesity and asthma in adolescents and young adults (NCT01027143) will help ascertain whether the type of fat in the diet is as important as the total amount of fat ingested.

**THE MICROBIOME**

In recent years, increasing attention has been paid to the interactions between the microbiome and the host’s immune system, with the hypothesis that altered microbial composition – or altered interactions with the microbiome – predisposes to the development of non-infectious diseases, including asthma and obesity. Frequent antibiotic use during pregnancy or in infancy has been associated with both obesity and asthma\textsuperscript{80,81}. Several longitudinal cohorts have shown that changes in gut microbial composition, diversity, or abundance in the first few months of life may increase the risk of wheezing or asthma\textsuperscript{82}. These changes may be in part determined by genetic predisposition, dietary patterns, and/or environmental exposures. Changes in the gut microbiome may lead to increased risk of obesity and asthma via several pathways, including dietary fibre fermentation and production of short-chain fatty acids\textsuperscript{83}. Whether the overall composition of the bacterial ecosystem or the abundance of specific bacterial species modulates the risk of atopy and asthma is unclear\textsuperscript{84}, and there is ongoing debate regarding the best methods to ascertain bacterial quantity and diversity for microbiome studies\textsuperscript{85}.

Whether microbiome changes associated with asthma are causal, coincidental, or the product of confounding, however, is unknown. Probiotic supplementation in early life (\textit{in utero} and early infancy) may help reduce the risk of atopic sensitisation and eczema, but may not help prevent asthma\textsuperscript{86,87}. An ongoing trial of supplementation with bacterial extracts in infancy (NCT02148796) could help clarify whether manipulation of the gut flora (or modulation of the interactions between the gut flora and the immune system) reduces the risk of asthma. Likewise, a small pilot study is currently underway to study the effect of probiotic supplementation to modulate the airway microbiome in obese asthmatic adults (NCT03157518); this study may help understand whether modulation of the
airway microbiome in obese asthmatics leads to improved asthma outcomes.

**GENETICS AND GENOMICS**

With both diseases having a substantial hereditary element, investigators have long hypothesised that there might be shared genetic variants that confer risk for obese asthma. Arguably, this genetic predisposition may be stronger in childhood, when long-term external factors have had less cumulative effects on overall health and disease status. Initial candidate gene studies yielded some encouraging results, including the genes for protein C kinase alpha (PRCKA) and leptin (LEP). The gene for the beta-adrenergic receptor 3 (ADRB3) was also reported to modify the association between obesity and asthma. Arguably, this genetic predisposition may be stronger in childhood, when long-term external factors have had less cumulative effects on overall health and disease status. Initial candidate gene studies yielded some encouraging results, including the genes for protein C kinase alpha (PRCKA) and leptin (LEP). The gene for the beta-adrenergic receptor 3 (ADRB3) was also reported to modify the association between obesity and asthma. The advent of genome-wide association studies (GWAS), however, did not add considerably to the list of potential candidates. The largest GWAS to date, which included upwards of 23,000 children and adults, reported gene DENN-domain containing 1B (DENND1B, also known as connec-denn 2) to be associated with BMI among asthmatic children; however, the main single nucleotide polymorphism (SNP) in replicated in only two of seven independent cohorts. Thus, it may be that the putative shared genetic link between obesity and asthma is more complex or arises from mechanisms other than single genetic variants. For example, a gene-by-environment analysis reported SNPs in the 17q21 locus that were associated with excess weight only among subjects with asthma and obesity; a recent analysis reported that an inversion in locus 16p11.2 conferred increased susceptibility to both asthma and obesity; this inversion was found near candidate genes for both asthma (type 1 IFN and IL-27) and obesity (SH2B1 and APOB48R). Moreover, a recent pilot study of 32 children found differences in DNA methylation profiles in peripheral blood mononuclear cell (PBMC) between children with and without obesity and asthma.

**THE CHALLENGE OF BMI**

Many challenges remain in our quest to understand the obese asthma phenotype (Table 1). While a preponderance of evidence (both observational and experimental) supports an association between obesity and incident or worsening asthma, these results are by no means homogeneous. For epidemiological studies, one of the difficulties stems from our definition of obesity. While simple and convenient, BMI may not be reliable or accurate, particularly in childhood and adolescence. The formula we use (weight/height$^2$) was proposed in the 1830s to describe “the average man” rather than to study obesity, and originally included various formulas (including weight$^2$/height$^5$ and weight/height$^3$) for different sex and age groups. The term “body mass index” –and its use to study obesity– did not happen until the 1970s and 1980s. Moreover, conversion to sex- and age-adjusted percentiles or z-scores may not suffice. For obese children and adolescents, BMI percentiles or z-scores correlate poorly with other measures of adiposity. Childhood obesity researchers have proposed different indicators, including the use of BMI as relative to the 95th percentile (either as a percent [%BMIp95] or as a difference [ΔBMIp95]) or as a difference [%BMIp95] + ΔBMIp95]. Others have proposed the use of a triponderal mass index (TMI, weight/height$^3$). In obese asthma research, this is reflected in several studies that have reported improved results.
when using markers of central obesity such as waist circumference or waist-to-hip ratio, neck circumference, skinfold-derived calculations of body fat, ultrasound, or dual-energy X-ray absorptiometry (DXA). Improved ways to evaluate obesity, as well as increased recognition of different adiposity distribution patterns, may improve our understanding of the impact of obesity on asthma.

**THE QUESTION OF SEX**

As is the case with many conditions, sex is an important modifier in both asthma and obesity. Asthma incidence is higher in boys than in girls until puberty/adolescence but becomes higher in women than in men afterwards. Likewise, many have reported sex-dependent associations between obesity and asthma outcomes. Some studies have reported that high BMI or other measures of obesity are associated with asthma in boys but not in girls, while others have reported associations only in girls, some have even proposed a distinct asthma phenotype in obese girls with early menarche. Furthermore, we and others have reported that the effect of obesity on lung function appears to be more pronounced among boys. However, it is still unclear whether these inconsistencies are the result of differing populations, or whether some characteristics or sub-phenotypes of obese asthma truly differ by sex. For example, alterations in the production or effect of sex hormones may mediate some associations seen in obese asthma and may partly explain why some sex associations vary according to age. In either case, varying proportions of males and females could potentially explain inconsistent results across studies.

**THE ISSUE WITH CAUSE AND EFFECT**

Most epidemiological observational studies are only able to report associations, rather than adjudicate causality. While many large, longitudinal studies have demonstrated that obesity (or increased adiposity) often precedes incident asthma, this does not preclude the possibility that both diseases might be consequence of an earlier cause (for example, early-life exposures, changes in the microbiome, or alterations in the immune system). Mendelian randomization studies in both children and adults have demonstrated that BMI/obesity is causally associated with asthma risk. Furthermore, basic science research and experimental data have described causal pathways between obesity and asthma that are beyond the scope of this review. However, even this evidence does not fully explain the mechanisms by which obesity affects asthma risk.
not preclude that, in some groups, the relationship might be inverted. A recent study in over 2,000 children reported that those with asthma were at higher risk of incident obesity over ~10 years of follow-up\textsuperscript{104}, although in that study the risk of obesity was driven by children who were already overweight at baseline, in certain cases asthma may indeed be a risk factor for subsequent obesity. With increased attention to the obese asthma phenotype, other studies may report similar results, and we hope that such reports will help us understand whether these constitute specific sub-phenotypes of this syndrome.

Along with obesity-preceding-asthma and asthma-preceding-obesity, obesity in and of itself could lead to symptoms that mimic or confound asthma, such as shortness of breath and dyspnoea on exertion; these could in turn lead to a misdiagnosis of asthma when it does not exist\textsuperscript{105,106}. Finally, it could be that in certain people both diseases simply coexist, without necessarily worsening each other.

**THE QUEST FOR MANAGEMENT APPROACHES**

While considerable amount of research exists both on the clinical aspects of obese asthma and its potential underlying pathways, very little is known in terms of how to best manage these patients. We have reported that obese school-aged children with asthma have reduced ICS response, but a recent study reported that ICS use in obese preschool children with asthma was associated with fewer exacerbations and symptom days\textsuperscript{107}. There have been some suggestions that obese individuals with asthma may have a preserved response to leukotriene inhibitors\textsuperscript{108,109}, but others have shown that ICS are still more effective\textsuperscript{110}. More recently, studies in adults with severe asthma have reported that obese patients are less likely to respond to omalizumab, with reduced response in lung function, asthma control, and FeNO\textsuperscript{111}. It is important to note that most of these studies were based on post hoc analyses of trials that were not specifically designed to study the differential response between obese and non-obese asthmatics. To the best of our knowledge, to date there have been no clinical trials specifically designed to evaluate whether a higher dose or a specific treatment approach works better among obese children with asthma. Until we have such answers, most patients with obese asthma are likely to benefit from standard, guideline-based, stepwise asthma management, but providers should remember to closely and continuously assess each patient’s clinical response.

There have been very few RCTs of weight loss for children/adolescents with obesity and asthma\textsuperscript{112-114}, all with very small sample sizes, assessment of diverse interventions, and different outcomes. Yet these preliminary studies show that diet, exercise, or both, may indeed improve asthma-related outcomes in these patients. A handful of RCTs in adults have shown similar results\textsuperscript{115}. Hasegawa et al.\textsuperscript{116} showed that bariatric surgery in subjects with obesity and asthma led to 50-70% reduction in emergency room (ER) visits and hospitalisations for asthma in the two years following the surgery. Larger, multi-centre, RCTs with uniform interventions and standardized outcomes are needed to elucidate the best approach to obese asthma. Until then, it is critical for clinicians to not just manage asthma symptoms, but also to screen and decidedly manage overweight.
or obesity. The ability to participate in healthy physical activity is not only a goal of asthma management, but it should be particularly encouraged in patients with obese asthma.

Alternative approaches may also prove to be helpful. Some observational studies have reported that metformin, an antidiabetic agent, use is associated with improved asthma control and fewer exacerbations among adults with diabetes and asthma\textsuperscript{117,118}. More recently, metformin has been reported to improve obesity outcomes in children and adolescents\textsuperscript{119-121}. While preliminary, these results suggest that the use of metformin and similar medications could represent new agents for management of obese asthma. Similarly, IL-6 is associated with asthma severity in obese adults with metabolic dysregulation\textsuperscript{61} and thus biological agents that block IL-6 actions could prove to be clinically helpful. As we continue to expand our understanding of obese asthma, so will the potential therapeutic targets for our patients.

**CONCLUSIONS**

Obese asthma is a complex, heterogeneous phenotype with multiple underlying pathways. While recognition and understanding of obese asthma have markedly increased over recent years, several challenges remain (see Table 1). Future research should focus on such challenges:

- Improved assessment of obesity and obesity-related metabolic complications that predispose to obese asthma;
- Identification of obese asthma sub-phenotypes, including similarities and differences by sex across different age groups;
- Evaluation of the role of epigenetic regulation in obese asthma, in response to environmental factors among susceptible individuals;
- Study of microbiome changes that may link obesity to asthma, or that may independently predispose to both obesity and asthma;
- Larger clinical trials of weight management for obese asthma, using standardized definitions, approaches, and outcomes;
- Identification of alternate management approaches, including those aimed at ameliorating metabolic and inflammatory pathways in obese asthma.

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**CONFLICTS OF INTEREST**

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