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Obesity and Asthma in Children: Current and Future Therapeutic Options

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Abstract

With the childhood prevalence of obesity and asthma increasing, it is important for pediatric professionals to appreciate that obesity modifies the diagnosis and management of asthma. These disease modifications present challenges to clinical management, including decreased responsiveness to controller therapy and decreased quality-of-life compared to normal weight asthmatic children. While consensus guidelines do not currently suggest specific changes in asthma management for obese patients, management of some patients may be improved with consideration of the latest evidence. This Current Opinion article briefly summarizes what is known regarding the complex relationship between obesity and asthma in children, and discusses practical issues associated with the diagnosis and effective clinical management of asthma in obese children. On average, obese patients with asthma do not respond as well to inhaled corticosteroid therapy. Management approaches including weight loss and routine exercise are safe, and may improve important asthma outcomes. Asthma providers should learn to facilitate weight loss for their obese patients. In addition, pharmacologic interventions for weight loss in obese asthma, though not currently recommended, may soon be considered.

Origins of Pediatric Obese Asthma

Most pediatric professionals recognize that obesity and asthma symptoms are common conditions in children, with their individual prevalence rates in some countries reaching near 30% [1, 2]. The two conditions have been linked in many high-quality epidemiologic studies[3]. Controversy has surrounded the proposed mechanism of this association, but not surrounded the fact that obesity complicates the diagnosis of childhood asthma and its management. Longitudinal data clearly describe a pattern where obesity pre-dates and increases the risk for incident asthma [3-5], though the precise nature of this association remains unknown [3, 6-10]. It is unlikely that the causal mechanism relating the two conditions is both singular and homogeneous throughout the population, although the mechanism(s) are likely to depend on age, sex and other factors. In young children, rapid early weight gain may be a sign of somatic growth dysregulation that precedes impaired airway development and clinical wheezing [11-14]. This is consistent with reports of

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maternal obesity and gestational weight gain preceding an increased incidence of childhood wheeze[15]. Additional investigations involving maternal, pre- and post-natal somatic growth, lung growth and respiratory outcomes are needed to fully describe this early life developmental phenomenon.

Another practical but distinct question is whether asthma can pre-date and increase the risk for subsequent weight gain and obesity. In light of the heterogeneous nature of both conditions and the many modifying factors for each condition, it is likely that the direction of causality between obesity and asthma is not uniform for all patients. A bidirectional association between asthma and obesity is biologically plausible since many children with asthma avoid exercise [16-18], increase sedentary time[19], and receive treatment with oral corticosteroid medications – three factors which promote weight gain. Several investigators have now shown greater subsequent weight gain among asthmatics compared to non-asthmatics [20, 21]. Reduced activity in asthmatic children is not universal, and appears to depend on the attitudes and teaching of parents about the role of exercise in asthma control [16, 18-20, 22-24], and may also be affected by childhood emotional health[18, 24]. Larger highly characterized prospective cohorts will need to be further studied, particularly assessing the roles of physical activity, diet, genetics, depression and environmental exposures, to untangle the complexities of asthma and obesity.

Obesity and Asthma Characteristics

Asthma among obese children has been difficult to characterize. The term ‘obese asthma phenotype’ has been used in the pediatric literature, but its use may prove to be an oversimplification of a complicated and poorly defined relationship. Asthma phenotype describes the clinical characteristics typically relating to onset, atopy status, symptom pattern, and response to therapy. With advances in basic science, asthma should instead be considered a syndrome with multiple endotypes that are separated based on underlying molecular and developmental mechanisms[25, 26]. Asthma endotype (an abbreviation from endophenotype) suggests a subtype of asthma defined by a particular molecular or developmental mechanism. The term ‘obese phenotype’ in the context of asthma needs to be used with caution because obesity’s role as a mediator, or modifier, is still very unclear. An example of a possible obese-asthma endotype as mentioned above is the typically non-atopic child with early life weight gain and subsequent asthma-like symptoms. The underlying mechanism may prove to be impaired lung growth and altered airflow perception. Heightened airflow perception determined by higher symptom reporting in relationship to peak flow variability was a phenomenon we saw exclusively in obese (versus lean) children and not in adults [27]. This childhood endotype is very likely a distinct phenomenon from the late-onset obesity-related asthma commonly seen in women [28, 29]. However, it is unclear what portion of the nearly 2 million obese asthmatic US children fit the characteristics of this growth dysregulation-related endotype. A sizeable portion of obese asthmatics may have Th2 allergic asthma and subsequently gained weight due to environmental forces.

Several observational studies have attempted to discover and describe an obese asthma phenotype [27, 30-33]. The differences between lean and obese children with asthma have

been subtle, varied and inconclusive – most likely because these studies have contained a mixture of populations (early growth dysregulation endotype mixed with atopic asthmatics who subsequently became obese). On average, children with obesity and asthma report greater respiratory symptoms [34, 35] and respond less robustly to inhaled corticosteroids [36, 37].

Two large population-based studies have reported greater asthma severity among obese asthmatics based on either patient symptom reporting or physician reporting of diagnostic severity [38, 39]. Though these results come from excellent epidemiologic studies, they reflect subjective questionnaires or clinician diagnoses rather than objective measures of asthma and thus, may be vulnerable to biases. Obese asthmatic children and adults do generally report reduced asthma-related quality of life compared to normal weight asthmatics [22, 33, 38-46]. When highly-characterized pediatric cohorts are examined, very little obesity-related difference can be found [30, 47-52]. Unlike with adults, childhood obesity is often not associated with reduced vital capacity or total lung capacity [22, 30, 33, 51] (signs of a restrictive defect) which may be related to a shorter duration of obesity (compared to adults) or the limitations of a BMI-based system for defining obesity in children. In some cases when obesity is defined by BMI 95th%, obesity has been associated with greater (not smaller) lung volumes [53, 54] and a mild obstructive impairment in airway flows [46, 48, 53, 55, 56]. BMI may not be the most appropriate classification measure in assessing the relationship between obesity and asthma. For example, greater adiposity when measured by DEXA or skin fold plicometry does associate in with altered pulmonary mechanics and restrictive lung impairment[57-59]. Importantly, the current data in children do not suggest that obesity leads to a higher risk for allergic airway inflammation[60-64], atopic disease, greater airway reactivity, or severe exacerbation. Post-hoc data has shown that obesity is associated with reduced response to inhaled corticosteroids [44, 45, 47, 65-70] and low-dose theophylline [47], and a slightly improved response to montelukast [66]. Reduced steroid controller response has been shown in children[37], and may be related to reduced contribution of eosinophilic disease or true glucocorticosteroid resistance[67], or both.

Weight loss in Pediatric Asthma

No specific asthma guidelines exist for obese children. An obvious exception, though it has not been thoroughly studied for asthma therapy, is the recommendation for weight-loss. Weight loss is listed as evidence category grade B for persons of all ages by the National Asthma Education and Prevention Program – Expert Panel Report 3 and is also recommended in the Global Initiative for Asthma guidelines [71, 72].

The Effect of Weight loss in Pediatric Asthma. Promoting weight loss for the obese asthmatic patient is justified based on population-based evidence of improved longevity and quality-of-life, and reduced risk of several conditions that can complicate asthma control including esophageal reflux, obstructive sleep apnea and restrictive lung disease [73, 74]. Therapeutic weight loss in asthma was recently reviewed by Adeniyi and Young for the Cochrane Collaborative [75]. They focused on rigorously designed RCTs involving weight-loss interventions compared to either no intervention or an alternative intervention. Four

studies involving 197 adults were included in their analysis, and included combinations of supervised exercise, low calorie diets and anti-obesity drug (orlistat and sibutramine). The reviewers concluded that weight loss led to reduced asthma symptoms, rescue medication use, and a trend toward improved lung function. Though they concluded that there was a high risk for bias, there was insufficient data to make firm conclusions on safety, adverse effects, quality of life, health care utilization or other phenotypic characteristics of asthma. The reviewers called for better designed studies, especially in children.

Though more data is clearly needed, it is rational to expect similar improvements in symptom control among obese children who are able to lose weight. To date, only a few small weight loss studies for asthma have been conducted in children (Table). Van Leeuwen and colleagues recently performed an open-label 6-week diet-induced weight loss trial in 20 overweight 8-18 year old children with exercise-induced asthma[76]. Weight loss did not change exhaled nitric oxide or baseline spirometry. However, post-exercise decline in lung function was significantly lessened after weight loss, and asthma-related quality of life was improved. Leeuwen described a direct relationship between weight loss and lung function improvements following exercise.

Jensen and colleagues performed a small pilot RCT of low calorie intervention (versus delayed intervention) among 8-18 year old children with persistent asthma[77]. Counselors taught lessons in goal setting, food selection, serving sizes, managing set-backs, and identifying/avoiding problematic behaviors. Compared to the control group, the low calorie intervention group experienced a significant reduction in weight, BMIz and total body fat (fig 1a), but not any of the cardiometabolic markers. The intervention group lost an average of 3.4 kg (compared to a gain of 1.3 kg in controls) and experienced a significant reduction in residual volume and expiratory reserve volume (fig 1b) that did not reach significance versus the control group. The change in asthma control questionnaire (ACQ) was significant versus the control group (fig 1c) though there was imbalance in baseline ACQ between the two groups. Change in CRP was significantly reduced in the intervention group versus the control group and the change in BMI-z was directly associated with reduction in CRP and eNO. The authors attempted to understand the mechanism of improved asthma by exploring associations between change in BMI z with various outcomes. Dietary intervention did not affect eNO, blood IL-6, leptin or adiponectin, but there was a significant reduction in sputum lymphocytes and a trend toward reduced sputum %neutrophils in the intervention group. The authors noted an inverse relationship between %eosinophils and BMI-z score which raises the question whether the impact of weight loss depends on atopy status.

Da Silva and colleagues randomized 26 obese 15-19 year old children with asthma to either a year-long psychological, nutrition, exercise and medical intervention or educational control[78, 79]. Participants underwent psychological and nutritional counseling once a week, and exercised three times weekly. Lung function, anthropometrics, VO2max, asthma severity, fat percentage, and systemic markers (lepin, adiponectin, CRP) were measured at baseline, 6 months, and 12 months. The intervention group had significantly decreased body fat percent, visceral fat, weight and BMI compared to controls, and also displayed reduced leptin and CRP and improved asthma control and lung function. Increases in adiponectin in the intervention group associated with improved lung function.

Larger randomized controlled trials in children are needed that test a variety of different weight-loss strategies among homogenous and well-defined asthma cohorts. These studies may help establish the validity and durability of effect of weight loss, and also the mechanism of action in various clinical settings.

Exercise, dietary components and weight-loss drugs: Implications for Pediatric Asthma

The first line treatment for pediatric obesity is a family-based intervention that involves a combination of lifestyle strategies to reduce energy intake, increase physical activity, reduce sedentary activities, facilitate family involvement and modify current family dietary and activity patterns. A recent Cochrane review evaluated 54 randomized controlled trials for the treatment of pediatric non-asthmatic obesity, including physical activity, dietary, and behaviorally orientated treatment programs. Current evidence cannot recommend one strategy over another, but the review concluded that combined behavioural lifestyle interventions were statistically and clinically significant for establishing weight loss for obese children[80]. Additionally, a systematic review and meta-analysis of RCT of nonsurgical interventions for obesity in children found 61 trials with complete data[81]. The authors concluded that several drug therapies (including sibutramine and orlistat) were effective at reducing BMI over short durations. Exercise as an intervention among sedentary children to both reduce the incidence of asthma or reduce asthma severity has a grounded rationale[26, 82]. Reduced daily activity and exercise has been implicated as a potential cause of greater asthma morbidity[7, 82]. Very little investigation has been conducted to date regarding how exercise impacts pediatric asthma. One study in adult asthmatics showed that exercise was associated with improved asthma-related quality of life and reduced sputum neutrophils [83]. Exercise programs in children do improve aerobic capacity (VO₂max), but it is unclear if exercise improves lung function and airway reactivity in asthmatics. The effect of exercise on airway mechanisms such as inflammation and oxidative stress are also generally unknown. Regular exercise in small groups of asthmatic children have shown no increase in asthma symptoms or inflammation and found a trend toward reduced IgE [84] and reduced oxidative stress markers[85]. Exercise also may act synergistically with inhaled steroids to improve lung function[85]. Exercise has been variably effective on reducing bronchial reactivity among children with EIB[86]. Levels of serum leptin and adiponectin that are typically present with obesity were associated with bronchial hyperreactivity following exercise challenge in children with asthma[87]. For all of these reasons, clinicians should consider promoting routine exercise among obese children with asthma as a long-term therapeutic strategy to improve asthma control and quality-of-life.

Because obese children appear to have greater evidence of feeding disinhibition [88], greater fast-food and saturated fat consumption[89, 90], and a diet lower in nutritional content[91], alterations in dietary components may constitute an additional therapeutic opportunity for children with obesity and asthma. Several large epidemiologic studies suggest that particular dietary characteristics (fish, omega-3 fatty acids, fresh fruits, vegetables; low saturated fat content) contribute to both reduced risk for asthma[92] and improved control of existing

asthma. One example includes the CARDIA longitudinal study which showed that omega-3 polyunsaturated fatty acids (PUFA) intake was inversely associated with incident asthma among young adults [93]. Wood found young adult asthmatics developed airway neutrophilia and reduced bronchodilator response following a high-fat meal[94]. These findings may partially explain the excess symptoms and bronchodilator use described in many studies of obese asthmatics. Since inhaled corticosteroids have limited potency against neutrophil-driven asthma, these results also provide mechanistic clues for why obese asthmatics respond poorly to inhaled corticosteroids. In addition, post-hoc analyses suggest increasing BMI is not associated with reduced effectiveness with montelukast. Therefore, montelukast should be considered for add-on therapy if asthma control is not achieved with ICS therapy alone.

Intake of omega-3 fatty acids may improve asthma control in obese asthmatics through a number of distinct anti-inflammatory mechanisms which has justified the funding of an ongoing trial evaluating its use specifically in obese asthmatics with persistent disease [95]. However, the most compelling data so far involves its use in preventing exercise-related symptoms. Exercise is one of the most common asthma triggers for obese children and adolescents[96]. Several studies now have found that pre-treatment with omega-3 PUFA supplements prior to exercise lead to reduced asthma symptoms and exercise-related drop in lung function [97, 98].

Currently no drugs are specifically recommended for obese asthma, and weight loss drugs are recommended in children only in circumstances with severe obesity-related complications[99, 100]. The impact of drug-induced weight loss on asthma is speculative. Changes in asthma outcomes have not been sufficiently studied with any weight loss drug, and should only be considered in cases of severe, refractory obesity and asthma. Orlistat (Xenical®, Alli®) is currently the only widely available and approved medication for simple weight loss in children and little is known about its effect on asthma. It is a synthetic derivative of lipstatin (a reversible gastric and intestinal lipase inhibitor) that is available over-the-counter or by physician prescription. Orlistat impairs triglyceride hydrolysis and can block up to 30% of fat absorption in the diet. Orlistat in many patients will reduce serum low-density lipoprotein and total cholesterol, and improve glycemic control. GI side-effects can limit adherence and the drug's longterm effectiveness, and there is limited safety data beyond two years. One large 54 week placebo controlled study in obese adolescents showed a mean BMI decrease of 0.55 kg/m² (versus increase of 0.31 kg/m² in placebo-treated) and 26.5% of orlistat-treated adolescents achieved at least a 5 kg weight loss (versus 15.7% in the placebo-treated). Orlistat was associated with a negative iron balance in obese adolescents, though no change was seen over 21 days in calcium, copper, magnesium, phosphorus or zinc. Patients below the age of 18 are not encouraged to use self-directed, over-the-counter treatment.

Metformin is another drug that requires further investigation in the setting of obese asthma. Now, metformin is commonly prescribed to obese adolescents with obesity and type 2 diabetes, but it is not specifically approved for use in children for simple weight loss. It is a biguanide oral agent that is generally well tolerated and is very effective at reducing circulating blood glucose among insulin resistant individuals by reducing hepatic glucose

release and increasing peripheral glucose uptake. Metformin, when given to obese children typically results in significant weight loss by means of increasing satiety and decreasing intestinal nutrient absorption. Metformin acts primarily by inhibiting mitochondrial respiratory-chain complex 1, leading to reduced ATP production[101, 102]. The resulting increase in the cellular AMP/ATP ratio leads to several downstream effects including direct inhibition of gluconeogenesis and activation of AMP-kinase. It is important to note that the studies evaluating metformin in children have been few in number, small in size and short in duration. A recent meta-analysis of 5 studies involving adolescents showed a BMI reduction versus placebo of 1.42 kg/m²[103].

The fact that metformin promotes weight loss and may have several beneficial mechanism relevant to lung health, makes it an attractive target for future investigation (figure 2). Metformin is an AMP-activated protein kinase (AMPK) activator that has been shown to dampen a variety of inflammatory processes [104] involved in cystic fibrosis [105] and LPS-triggered airway inflammation[106]. AMPK has also been shown to induce macrophage polarization to an anti-inflammatory phenotype [107] which may be particularly important in obese asthma[108]. Recently, overweight/obese asthmatics were demonstrated to have alveolar macrophage polarization to an inflammatory phenotype [108]. Limited lung mechanistic data exist regarding the impact of metformin on asthmatic lung inflammation. One obese-asthma animal model using the trigger of acute ozone exposure found that metformin did not reduce the innate airway hyperresponsiveness and increased airway responses normally seen in obese mice [109]. However, in a chronic asthma model utilizing a different trigger (ovalbumin and fungal-associated allergenic protease), metformin reduced several asthma-related processes including eosinophilic and neutrophilic lung inflammation, peribronchial inflammatory cell infiltration, IgE responses, airway smooth muscle thickness, remodeling-related growth factor expression and airway oxidative stress [110]. In a separate study, metformin also eliminated the normal elevations seen in eotaxin, TNF-alpha, NOx and iNOS expression following murine ovalbumin sensitization and challenge[111]. Shore and colleagues in a study of human airway smooth muscle showed that thiazolidinediones (and possibly metformin) inhibit the production and release of several asthmagenic inflammatory mediators from airway smooth muscle possibly through mechanisms unrelated to AMPK activation [112].

Conclusions

Nearly all aspects of obese asthma in children require deeper investigation. However, to best improve the overall health of obese children struggling with asthma, health providers would be smart to focus on factors and co-morbidities which might impede the successful implementation of current GINA-based guidelines. Examples include health literacy, clean air, sleep apnea and depression. New drugs aimed at weight loss or insulin resistance may become helpful in the future. For now, providers should focus on developing the resources to assist families in weight loss strategies that include increased exercise, reduced calories particularly from processed fast foods, and a focus on fish, fruits and vegetables.

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List of Abbreviations

ACQ Asthma Control Questionnaire

CRP	c-reactive protein
VO2max	maximal oxygen consumption
PUFA	polyunsaturated fatty acid
AMPK	AMP-activated protein kinase

Fig 1.

Effects of diet-induced weight loss in children with obesity and asthma. Change from baseline in: (a) Total Body Fat (%), (b) Expiratory Reserve Volume, (c) Asthma Control Questionnaire (ACQ) score. ‡P-value < 0.05 within group difference before and after intervention; § - P-value < 0.05 intervention change between groups. ERV – expiratory reserve volume, ACQ – asthma control questionnaire. Adapted from *Clinical and Experimental Allergy*, Vol 43, Jensen ME, Gibson PG, Collins CE, Hilton JM and Wood LG., Diet-induced weight loss in obese children with asthma: a randomized controlled trial, 43(7):775-84, 2013, with permission from Wiley & Sons.

Fig 2.

Effects of metformin relevant to lung health. Metformin gains intracellular entry mainly by various isoforms of organic cation transporters (OCT). It can act of a variety of cell types throughout the body and has been shown to reduce body weight, improve insulin sensitivity and limit inflammatory responses. OCT – organic cation transporter, LPS – lipopolysaccharide, HBE – human bronchial epithelial.

Table

Weight loss interventions in Children with Asthma

	cohort	Design	phenotype	intervention	outcome
Da Silva, 2012 ^[1]	Age 15-19, n=15 (20% male), Brazil	No randomization; not controlled	EIB	52 wks: low-cal diet, exercise, counseling	EIB prevalence went from 100% to 0%; significant reduction in post-exercise FEV1 drop
Da Silva, 2012 ^[2]	Age 15-19, n=26 (20% male), Brazil	No randomization; not controlled	Asthma, not defined	52 wks: low-cal diet, exercise, counseling	Improved lung volumes and FEV1/FVC; reduced symptoms; increased adiponectin associated with improved FVC
Jensen, 2013 ^[3]	Age 8-17, n=28; (61% male) Australia	Randomized intervention; Wait-list control group present	undefined	10 wk: low-cal diet	0.2 drop in BMI-z; improved ACQ; airway + systemic inflam did not ; in BMI was assoc with in CRP and eNO
Van Leeuwen, 2013 ^[4]	Age 8-18, n=33 (75% male), The Netherlands	No randomization; not controlled	EIB	6 wks: low-cal diet	↓FEV1 drop after exercise test; improved PAQLQ, no change in spiro or FENO

BMI – body mass index, TNF – tumor necrosis factor, ACQ – asthma control questionnaire, CRP – C reactive protein, eNO – exhaled nitric oxide, EIB – exercise-induced bronchospasm, FVC – forced vital capacity, FEV – forced expiratory volume in 1 second.

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