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PEDIATRIC REVIEW

Asthma and obesity in childhood: on the road ahead

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Epidemiological data show a link between asthma and obesity, suggesting many different mechanisms that may underlie the association. However, diagnosis of asthma is often self-reported by patients or caregivers. Definition of asthma is crucial, particularly in childhood. Obesity can be associated with symptoms commonly attributed to asthma, such as wheezing, dyspnoea and sleep apnoea. Obese subjects are less fit and may have more frequent bouts of breathlessness on exertion accompanied by an exaggerated symptom perception. Therefore, the link between the two diseases should be analysed by focusing not only on reported diagnosis of asthma but also on objective markers that can better characterize the asthma phenotype. These markers should include lung function parameters, bronchial hyper-reactivity, atopic sensitization and indices of lung inflammation. As we look back and move forward, a multidisciplinary approach is increasingly necessary to understand the complexity of obesity and asthma, keeping in mind that diet and exercise could influence both diagnosis and treatment. In the meantime, in clinical settings, physicians should be cautious about diagnosing asthma in obese children on the basis of self-reported symptoms alone and should confirm the diagnosis by using objective measurements and marker evaluations that can better identify asthma phenotype and exclude overdiagnosis.
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Introduction

Asthma is the most frequent chronic illness in childhood,[1,2] with increasing levels of morbidity in most of the countries worldwide.[2] Although a possible end to this epidemic[3] has been hypothesized, it is undeniable that in the past few decades the prevalence and severity of and the hospitalization rates for asthma have increased significantly in western countries.[3] Epidemiological studies on the same population at different times[4–8] have shown an increased prevalence of asthma in childhood. The prevalence of obesity has also increased with a parallel course over the past decades, representing with asthma two of the major worldwide child health priorities.[9–11] Epidemiological studies have pointed out the rapid changes in the prevalence of asthma and obesity occurring in westernized countries as well as in developing countries undergoing their epidemiological transition phase[12] in such a parallel way as to give support to a link between the two conditions. However, the reasons for the association between asthma and obesity are unknown. Suggested mechanisms include sedentary lifestyle, dietary factors, systemic inflammation and reduced chest wall compliance by obesity, insulin resistance, comorbidities and common genetic predisposition.[13–18]

Epidemiology-based evidence in childhood

Pediatric cross-sectional studies have reported a link between asthma and obesity,[13–29] but the strength of the link is, however, rather low with a reported relative risk ranging in most studies from 1.5 to 3.0.[30–32] Therefore, in the likely event that the link between asthma and obesity is a rather specific phenomenon, low or negative outcomes may result from a dilution or an absence of the relevant subset in the population sample studied.[31] This effect, showing no association between overweight and asthma, was evident in three studies that evaluated the association in a rather small subset of African-American adolescents,[28] in a large cohort of Canadian children but under 11 years of age[16] and in a group of Italian children.[29] In the Canadian study, a maternal report of current diagnosed asthma was not associated with being overweight.[16] Furthermore, in these cross-sectional studies, obesity and asthma were one of the factors among others that were analysed simultaneously, and it is impossible to disentangle the cause and effect.[33]

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However, several longitudinal studies in children and adolescents showed positive results for an association, and in particular, they support an association between body weight and the future risk of asthma.[32] A study on a Tucson birth cohort found that overweight or obesity at 11 years of age was associated with unremitting asthma after puberty.[34] The girls, but not the boys, between 6 and 11 years who were obese or overweight presented a sevenfold risk of developing asthma than those who were of normal weight.[35] New-onset asthma associated with overweight or obesity was observed by Gilliland *et al*.[36] with a relative risk of 1.52 and 1.60, respectively. Mannino *et al*.[37] showed that boys but not girls with body mass index (BMI) >85th percentile were at an increased risk of developing asthma later on. Recently Mamun *et al*.[38] found that increased BMI *z*-scores between the ages of 5 and 14 years were associated with increased risk of asthma symptoms in adolescence, with a stronger, although not significant, association in the males. In this study, the relationship remained robust with adjustment for a range of reasons in early-life exposure such as a child's weight at birth, length of breastfeeding, maternal lifestyle during pregnancy, as well as diet, sports and TV watching at follow-up at 14 years.[38] Finally, in another study, the annual variations in BMI *z*-scores were significantly associated with asthma in girls.[39]

Atopy is another important hallmark of childhood asthma as at least 90% of asthmatic children present clinically determined allergic sensitization.[40,41] Therefore, an association between obesity and atopy has also been hypothesized. However, only a minority of studies evaluated the link between obesity and atopy, leading to prevalent negative results for the association.[31] Negative results for an association were obtained by von Mutius *et al*.[21] in the National Health and Nutrition Examination Survey study that assessed more than 7500 children, in which the researchers found a positive link between BMI and asthma and use of asthma medications but failed to show any relationship between overweight and atopy. Similar results were obtained in New Zealand where BMI was correlated to wheezing but not to atopy or bronchial hyperresponsiveness.[14] Eneli *et al*.[42] did not find any association between atopy or allergic rhinitis and BMI in German children. Gold *et al*.,[39] using BMI as a predictor of incident new-onset asthma in a 4-year follow-up, showed a higher risk of asthma in children who were overweight at recruitment, but this effect was limited to non-allergic children. Garcia-Marcos *et al*.[43] showed that obesity was a risk factor for current severe asthma in both boys and girls independently from the occurrence of rhinoconjunctivitis, concluding that obese 6- to 7-year-old children are more at risk of suffering from non-allergic asthma than the non-obese subjects. Finally, in 1576 Belgian schoolchildren aged between 3.4 and 14.8 years, an increased prevalence of allergic sensitization was found but only in underweight girls, again showing no correlation between weight and allergic respiratory symptoms, eczema or rhino-conjunctivitis.[44]

Asthma and obesity: more than a spurious association

Although obesity may simply be a marker of lifestyle habits also associated with asthma, several specific mechanisms can be proposed for their association.

Mechanical airway changes in obesity

In the obese patient, the tidal volume (TV) and functional residual capacity are decreased due to changes in elastic properties of the chest wall.[45,46] Retractile forces of the lung parenchyma on the airways are reduced at low lung volume. At low functional residual capacity, the airway smooth muscle may be unloaded with a paradoxical increased shortness in response to normal parasympathetic tone or to other bronchial-constricting agents.[47] Thus, it has been hypothesized that in obese patients, breathing at low TV does not allow the normal stretching of airway smooth muscle during breathing, which causes detachment of actin–myosin crossbridge of the airway smooth muscle. The bigger the TV, the greater the ensuing bronchial dilation.[48] This fact, known as 'deep inhalation effect', allows restoration of the dilation of the airways in normal conditions. This protective effect is reduced in asthmatics and also in obese individuals in comparison to lean controls.[49,50] Therefore, the net result in the airways of the obese subjects would be more substantial airway smooth muscle contraction and airway narrowing.

Additional mechanical factors may involve a mechanism of uncoupling the airways from the retractile forces of the lung parenchyma due to the repeated chronic small airway closure observed in many obese patients breathing at low TV. Repeated opening and closing of peripheral airways may determine the rupture of alveolar attachments to bronchioles that lead to exacerbation of the airway narrowing.[51]

From a clinical point of view, even if a clinically significant restrictive pattern (total lung capacity <85% predicted) is usually observed only in massive obesity, in general in obese subjects the ability to respond to natural stress, such as exercise that is so common in children, is hampered by small TV, causing altered smooth muscle contraction and impaired lung function. Even though it has been suggested in adults that the peak exercise capacity is normal in otherwise healthy obese subjects,[52,53] it is not surprisingly that exercise capacity is often impaired in obese children. This can be due to the increased work of breathing with the resulting increased perception of breathing effort and dyspnoea.

Chronic inflammation in asthma and obesity

Both asthma and obesity are recognized as pathological conditions characterized by systemic inflammatory state. By definition, asthma is an inflammatory disease with infiltrating eosinophils, lymphocytes and other cells associated with airway hyperreactivity (AHR) and remodelling of

the airways with thickness of the lamina propria and loss of elasticity and consequent lung function impairment.[54] These features have been shown to be present even in the airways of small infants with persistent asthma.[55,56]

It has been well established that obesity is also characterized by low-grade systemic inflammation that spills over into the blood of a series of mediators, known as adipokines, which induce an inflammatory activated state in organs distant to adipose tissue. Adipokines include interleukin-6, tumor necrosis factor-α, eotaxin, vascular endothelial growth factor and monocyte chemotactic protein that have been associated with asthma and may have a role in the common state of inflammation.[45] In obesity, the two main hormones involved in inflammatory balance and which are potentially relevant in asthma also are leptin and adiponectin.[45,57] Adiponectin has an important anti-inflammatory effect on obesity.[58] Leptin is pro-inflammatory and pre-treatment with leptin during allergen challenge of sensitized mice increased the allergen-induced AHR without an influx of eosinophils and T helper type 2 cytokine expression.[59] High levels of leptin have been associated with an increased lifetime prevalence of asthma, especially in non-atopic asthma.[60] In asthmatic patients, serum levels of leptin are high, independently from obesity,[61,62] leading one to consider that leptin may contribute to the inflammatory cascade typical of asthma or it could be the result of the systemic state of inflammation present in the disease.[45,63] Recent studies, however, seem not to support the hypothesis that adipokines mediate the association between obesity and asthma. In longitudinal cohort studies, there was no significant association between adipokines and any other markers of asthma, such as doctor diagnosis of asthma, bronchodilator response, airflow obstruction and exhaled nitric oxide.[64,65]

Role of physical activity

The parallel increase in asthma and obesity, although supported by many causes, may be the result of the progressive decrease in levels of physical activity and adoption of a more sedentary lifestyle that has been observed in western countries in recent decades.[30] This change in lifestyle, influenced by a constructed environment and accompanied by lack of safe areas for physical activities, a greater use of television, computer and video games and increased food and calorie intake, represents a real public health priority.[66] Obesity may be associated with a lack of fitness and may contribute to breathlessness, which could easily be interpreted by the subject as asthma or wheezing. The presence of symptoms may determine an exclusion of the physical activity that in turn can increase the sedentary lifestyle and increase in overweight.[67] The Childhood Asthma Management Program study showed that in mild-to-moderate asthmatic children, there was a significant risk of becoming overweight. Being overweight for asthmatics was associated with lower intelligence quotient, more social withdrawal and greater internalized psychological distress.[68] Furthermore, as the children became older the overweight group showed increased evidence of behaviour problems and further decreased physical activity.[68]

The relevance of asthma definition

To establish the relevance of a link between obesity and asthma, it is essential to have a precise definition of asthma. In epidemiological studies in children, current asthma is often defined as parent/guardian-reported diagnosis of asthma and asthma-related symptoms, use of medications or emergency care access in the previous 12 months. Thus, a diagnosis of asthma is often based on non-objective measures that will assure more weight to the strength of the diagnosis. When the definition of asthma is revised, as suggested by international guidelines,[69] to include more stringent clinical characteristics of childhood asthma, such as bronchial reversibility to bronchodilator, AHR, atopy and bronchial inflammation, the association between asthma and obesity seems to be less consistent, with very few studies confirming the symptom history by objective measurements. Although self-reported asthma (even if doctor diagnosed) is valid for epidemiological purposes, it is reasonable to believe that some of these patients with 'asthma' may have respiratory symptoms due to obesity, but may not meet rigorous objective physiological criteria for asthma, falsely inflating the number of new cases of asthma in obese subjects.[70,71] Lack of bronchodilator response may indicate a fixed airway obstruction or a near-normal function during testing. In such cases evaluation of AHR by methacholine or exercise test is useful.[72] Furthermore, demonstration of bronchial inflammation not only supports the diagnosis but also defines the asthma phenotype and defines the disease control.[72] Noninvasive tests, such as exhaled nitric oxide and induced sputum cytology, can be easily applied even in childhood to evaluate the bronchial inflammatory condition of the subject, showing increased values and eosinophilic or neutrophilic prevalence in atopic and in non-atopic asthma, respectively. Therefore, there is evidence to support an association between obesity and asthma defined by symptoms, doctor diagnosis and medication use but very little evidence to support a link when the objective markers previously indicated are used for the diagnosis.

Castro-Rodriguez *et al*.[35] in their longitudinal study also evaluated the bronchodilatory reactivity (variation of forced expiratory volume in 1 s (FEV_1)) and peak flow variability in overweight girls. These objective measurements of lung function varied significantly in obese girls when compared with normal-weight girls, leading the researchers to consider that there may be an 'anomaly' in the regulation of the bronchial tone at this age in overweight. In adults with mild-to-moderate persistent asthma, analyses of parameters by normal–weight versus overweight/obese asthmatics showed

only very small differences in FEV_1, FEV_1/forced vital capacity, rescue albuterol use and asthma-related quality of life.[73] The researchers stated that increased BMI is not associated with clinically significant worsening of impairment in subjects with persistent asthma.[73]

Regarding AHR in a recent birth cohort study, Scholtens *et al*.[74] analysed reported weight and height, reported wheeze and dyspnoea and evaluated AHR at age 8 years by methacholine challenge. They found a significant increased risk for dyspnoea but not for wheezing in children who were overweight at age 6 to 7 years. They found a very high prevalence of increased AHR in the whole population (40% of subjects), significantly associated with overweight/obesity (BMI >85th percentile) at age 6–7 years. They concluded that children with a current high BMI are at increased risk to have dyspnoea and AHR at age 8 years.[74] However, in the editorial accompanying the study, it was emphasized again that dyspnoea in overweight children may not always be asthma.[75] The failure to show significant relationships between BMI and wheeze, BMI and inhaled corticosteroid prescription and BMI and rest dyspnoea might support the hypothesis that the dyspnoea was primarily caused by factors other than asthma.[74,75] Another long-term post-bronchiolitis follow-up study did not find any increased risk for AHR, as evaluated by exercise challenge, in overweight children.[76] Furthermore, two previous studies did not observe increased prevalence of AHR among children with a high BMI. In a large cohort of Israeli children, obese subjects presented more wheeze, more physician-diagnosed asthma and more use of inhaled drugs than non-obese children.[15] However, AHR was significantly greater among the non-obese than in the obese children. Results obtained in the Childhood Asthma Management Program study showed higher BMI associated with lower lung function parameters but not with AHR.[77]

Obesity and asthma control relationship

Previous data have hypothesized that obesity is associated with a more severe asthma phenotype, particularly in adults.[78,79] However, in childhood, very often asthma in obese patients must be considered as more difficult to control rather than severe. Difficult asthma is defined as that what is poorly controlled (reported recurrent symptoms, frequent exacerbations, daily activity limitations, repeated hospital admissions, and so on) despite optimal medical treatment.[72,80] Difficult asthma can occur in patients with objectively mild, moderate and severe asthma. In difficult-to-control asthma there is a disconnection between patient expectations and outcome. Some patients can become over-reactors, taking excessive doses of treatment for their objective level of abnormality and thus running the risk of increased drug side effects.[80] Children with difficult-to-control asthma can present different contributing factors, such as allergen or smoke exposure, presence of psychosocial factors, of sedentary life and overweight or obesity and of coexisting pathologies. Their asthma may not be controlled simply because medications are not taken. In difficult asthma a re-evaluation of the diagnosis is mandatory.[72] Objective asthma evaluation by spirometry, AHR testing and bronchial inflammatory marker investigation should therefore be particularly useful at this stage to better characterize the patient,[72,80] allowing to exclude asthma in some patients and to classify the severity of the disease in others.[81] Measuring asthma may have important implications, given the opportunity to show misdiagnosis of asthma that is otherwise based only on reported symptoms.[82,83] It has been shown that about one-third of obese and non-obese adults with physician-diagnosed asthma did not have asthma when objectively assessed, the risk of overdiagnosis being high.[81] In these cases, the absence of AHR and of reversibility is unusual in currently symptomatic asthma and would certainly suggest an alternative diagnosis.[72,84,85] Once all these issues have been addressed, there will only be a small group of children with real severe asthma despite conventional therapy.[72] Therefore, obese subjects may be more often symptomatic, require more asthma drug prescriptions, more urgent visits and hospitalizations for asthma and longer stays in the emergency room.[70,86–88] Sin *et al*.[70] showed an increased risk of asthma in obese subjects, greater use of bronchodilators and dyspnoea, but with no association with more deterioration of airway obstruction in obese subjects when compared with normal-weight subjects. Dyspnoea is often a complex psycho-physiological symptom characterized by subjective sensation of an increase in the perceived work of breathing, especially during exercise. Dyspnoea in obese children could unmask other associated conditions, such as respiratory and heart diseases. This leads to consider that obesity may more likely influence an asthma symptom perception and modify the asthma control through co-morbid illnesses that are associated with asthma, such as gastroesophageal reflux and obstructive sleep apnoea.[72,80] These conditions must be analysed and excluded in childhood also as they are present in the overweight and are themselves associated with asthma and wheeze.

Gastroesophageal reflux is a common medical condition and often coexists with asthma and obesity even in childhood. A case series of 33 children undergoing evaluation for difficult asthma revealed an abnormal pH study in 73% of subjects,[89] leading to consider that sometimes a 6-month trial of anti-reflux medication may be indicated in those patients with suggestive clinical history and unresponsive symptoms.[72]

It has been shown in children that the sleep-disordered breathing may partly explain the link between obesity and asthma: children with active wheezing not only have a significant higher prevalence of obesity but also more frequent obstructive sleep apnoea.[13] Indeed, obesity *per se*, is a well-recognized risk factor for obstructive sleep apnoea.[82,90] Increased fat tissue deposition in the pharyngeal

region and reduced operating lung volumes in obesity together exert an effect to reduce upper airway calibre and to increase their collapsibility; airways are thus predisposed to repetitive closures during sleep.[82,91] It has also been shown that in overweight children both habitual snoring and obstructive sleep apnoea syndrome are associated with increased airway inflammation, measured as exhaled nitric oxide.[92] However, in the absence of sleep-disordered breathing, the level of nitric oxide was within the normal range, excluding one of the indicated hallmarks of asthma.[92]

Conclusions

Overweight or obese children often report greater limitation of physical activity with higher asthma-impairment scores than normal-weight peers, although pulmonary function tests were not different.[93] Overweight asthmatic children may perceive their asthma as worse and experience greater limitation of physical activity; for this reason, they receive more drug prescriptions and use more asthma relievers.[82,93] Overweight asthmatic children are significantly more likely to be admitted to the hospital, regardless of presenting clinical asthma scores and therapeutic interventions.[88] Obesity increases the work of breathing and decreases lung volumes, giving to the patient the perception of more dyspnoea and asthma-like symptoms that may be more likely misdiagnosed by their physicians.[75] Dyspnoea, especially during exercise in obese patients, should not always be considered a manifestation of asthma or of exercise-induced bronchoconstriction, but it should be considered in the differential diagnosis of dyspnoea including normal physiological exercise limitation, vocal cord dysfunction, hyperventilation syndrome or deconditioning.[72] Deconditioning is a common cause of dyspnoea and is quite frequent in sedentary, overweight children who do not present asthma but who have symptom-like bronchospasms and could be overdiagnosed. Therefore, childhood overweight may represent a significant health effect as excessive body weight is associated with additional loss of quality of life in children with asthma.[94]

What came first?

By reviewing pediatric literature, we can conclude that obesity increases prevalence and incidence of asthma and at the same time reduces asthma control. We have described several mechanisms that could explain this relationship, among which we stressed lung volume and reduced TV, low-grade systemic inflammation, changes in adipose-derived hormones, obesity co-morbidities that exacerbated asthma and a share of common aetiology, in particular, low physical activity and perhaps a sedentary lifestyle in general.[65]

Novel treatment and new therapeutic strategies for the treatment of obese subjects with asthma may result from an increased understanding of the mechanisms underlying this relationship.[95] In conclusion, it is not simple or clear what came first and what interacts more and finally whether it is impossible to disentangle the cause and effect of both diseases. In light of this conclusion, a multidisciplinary approach is increasingly necessary for understanding the complexity of obesity factors and asthma.

Conflict of interest

The authors declare no conflict of interest.

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