Vol. 1(2), 67-73, 2023

PEDIATR RESPIR J

REVIEW

Pediatric obesity-related asthma

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10.56164/PediatrRespirJ.2023.16

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ABSTRACT

There is significant epidemiological and experimental evidence of an association between obesity and asthma, both in children and adults. Children with obesity and asthma suffer from greater severity, worse symptom control, and overall lower quality of life. In this review, we examine some of the evidence relevant to pediatric "obese asthma", some of the underlying mechanisms, including the impact of obesity on lung function, systemic and airway inflammation, insulin resistance and the metabolic syndrome, and the role of genetic predisposition and genomic regulation. We then briefly review current recommendations for the management of these children, including in the management of their asthma and evidence for weight loss interventions. Finally, we highlight gaps and future directions to further our understanding of obesity-related asthma and to improve our management of asthma in these children.

IMPACT STATEMENT: Obesity can have a significant impact on asthma risk, morbidity, and severity. Understanding the underlying mechanisms of "obesity-related asthma" will help us better care for children and adolescents with this phenotype of asthma.

KEY WORDS

Childhood asthma; obesity-related asthma; obese asthma.

INTRODUCTION

Asthma is the most common non-communicable disease in children (1). It affects over 4.2 million children in the US, leading to over 790,000 emergency department (ED) visits and more than 64,000 hospitalizations every year (2). In Italy, the prevalence of pediatric asthma ranges around 9.5% to 10.5% (3). Given its high prevalence and disease burden, much work remains to improve management and quality of life for patients with asthma around the world (4). Obesity is a major public health problem. More than 340 million school-age children and adolescents worldwide are obese (5). In the US, ~22% of youth ages 6-19 years are obese (defined as a body mass index [BMI] ≥95th percentile for age and sex) (6). Over the past few decades, mounting evidence has pointed towards an effect of obesity on asthma risk and severity (7). In this article, we will examine some of the epidemiological and clinical evidence of a pediatric "obese asthma" (or "obesity-related asthma") phenotype (**Infobox 1**). This review is based on studies discussed during the XXVI Congresso Nazionale SIMRI in Palermo, October 27th-29th, 2022.

Infobox 1. *Mechanisms and pathways that underlie or contribute to "obesity-related asthma" in children.*

- Changes in airway anatomy, respiratory mechanics, and lung function.
- Systemic and non-atopic inflammation.
- Insulin resistance, the metabolic syndrome, and hyperlipidemia.
- Immunologic alterations and dysregulation.
- Dietary and nutritional changes.
- Sex hormone alterations.
- Changes in the microbiome.
- Effect modification of environmental exposures.
- Decreased response to asthma medications.

EPIDEMIOLOGY OF OBESITY AND ASTHMA

Several longitudinal epidemiological studies have reported that obesity (or accelerated weight gain) is a risk factor for incident asthma later in life, as well as for worse asthma outcomes (8-17). We previously reported that maternal obesity during pregnancy, as well as excess weight gain, are associated with higher risk of recurrent wheezing and asthma in the mother's offspring (18), suggesting that even *in utero* exposures may lead to the increased asthma predisposition seen with obesity. Among children who already have asthma, obesity is associated with worse disease severity, more frequent and severe exacerbations, poor symptom control, lower asthma-related quality of life, and a higher risk of requiring intubation and mechanical ventilation (19-23). Children with obesity and asthma may also have a reduced response to asthma medications, including bronchodilators and inhaled corticosteroids (ICS) (24, 25). Much like obesity and asthma, "obesity-related asthma" is a complex and multifactorial phenotype, underpinned by several contributing mechanisms. The relative contributions of each pathway differ among patients, and are likely distinct between children, adolescents, and adults.

OBESITY AND LUNG FUNCTION

Obesity can have a significant effect on pulmonary function, and this effect probably differs depending on the individual's age, developmental stage, degree, and duration of obesity, and whether they have asthma or not (26). In adults, likely as a function of the amount of excess weight and the duration of their condition, obesity has been associated with a restrictive deficit characterized by low lung volumes, symmetrically reduced FEV1 and FVC, and a normal FEV1/FVC ratio (27, 28). In children, however, higher weight or higher BMI has often been linked with higher FEV1 and FVC, and with lower FEV1/FVC ratios (29-31). In a large meta-analysis, we reported that age indeed modifies the association between obesity and spirometry measures: overweight/obesity was associated in adults with symmetrically reduced FEV1 and FVC, resulting in a normal FEV1/FVC ratio; whereas in children there was a lower FEV1/FVC with normal or slightly higher FEV1 and FVC (32). In a cohort of children with asthma, those who were not obese during the initial period of ~4 years but became obese afterwards had significant decreases in FEV_1 and FEV_1/FVC (but no significant changes in FVC) by ~26-30 years of age, compared with those who never became obese (33). We recently reported an increased prevalence of airway dysanapsis in overweight and obese children with and without asthma (34). Dysanapsis describes an asymmetry between the growth of the diameter of the airways and the volume of the lungs. For instance, breath-hold divers who "hyper-inflate" their lungs in order to provide extra oxygen and pressure protection, exhibit dysanapsis due to their larger lung volumes but normal airway size (35). In children with and without asthma from several cohorts, we reported that higher BMI was associated with normal or supra-normal FEV1 and FVC, with larger increases in FVC leading to a low FEV1/FVC ratio (34). Of interest, among obese children who had asthma, dysanapsis was associated with worse asthma symptoms, exacerbations, and medication use.

OBESITY AND AIRWAY INFLAMMATION

Obesity has been associated with a systemic pro-inflammatory state, which is likely responsible for at least some of the comorbidities and complications seen in obese children and adults. Investigators have therefore suggested that obesity-related asthma may stem from a systemic (non-atopic) inflammatory state, rather than the localized atopic inflammation of the airways seen in most children with asthma. Children with obesity and asthma have elevated Th1 responses, and such association may be medicated by metabolic dysregulation (36, 37). Yet, other studies have reported links between obesity and atopic sensitization (38, 39). In an analysis of data from adolescents in the U.S. National Health and Nutrition Examination Survey (NHANES), we found that obesity was associated with asthma only among youth

without evidence of eosinophilic airway inflammation, but that in adolescents who already have asthma, being obese and having high FeNO synergistically worsened asthma control and severity (40). Similar results were reported for obesity and rhinitis (41). This suggests that both Th2 and non-Th2 inflammatory responses may play a role in obesity-related asthma.

INSULIN RESISTANCE AND METABOLIC SYNDROME

Insulin resistance, metabolic dysregulation and the metabolic syndrome, and chronic dyslipidemia lead to many complications of obesity. Insulin resistance is more prevalent in children with asthma than in healthy children (42, 43), and metabolic dysfunction may be more important in pediatric obesity-related asthma than the mere amount of excess fat (44). We previously reported that insulin resistance is associated with lower FEV1 and FVC in adolescents independent of asthma, and that the metabolic syndrome is associated lower FEV1/FVC, with the effects being worse among adolescents with asthma (**Figure 1**) (45). More recently, analyses of the Tucson and Avon cohorts reported that higher blood insulin level in early childhood may be linked to higher asthma risk in adolescence and young adulthood, independent of BMI (46).

GENETICS AND GENOMICS

Both asthma and obesity have an important hereditary component. Initial candidate gene studies looking at both asthma/wheezing and BMI or obesity reported potential genes, including PRKCA (protein C kinase alpha), LEP (leptin), and ADRB3 (beta-adrenergic receptor 3) (47-49). With the era of genome-wide association studies (GWAS), a study of 23,000 children and adults reported gene (DENND1B) to be associated with BMI among asthmatic children (50). More recently, two studies in adults have found other loci associated with asthma and obesity phenotypes: a large cross-trait GWAS of more than 450,000 adults in the UK Biobank (51), a subsequent GWAS of over 300,000 subjects (52). Mendelian randomization (MR) studies have also been used to investigate the link between obesity and asthma. MR studies are based on the principle that certain diseases have a strong genetic component, and therefore constructing genetic panel of SNPs strongly associated with obesity,

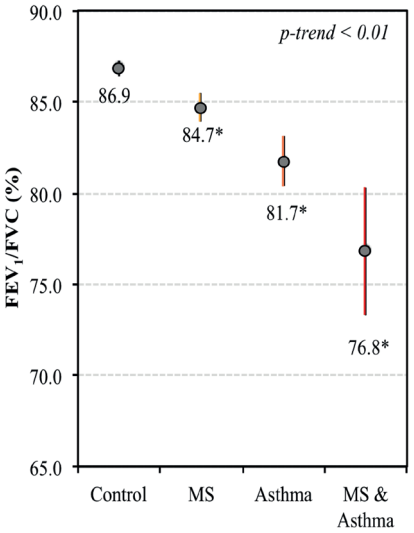

Figure 1. *Predicted FEV1/FVC in NHANES adolescents, by asthma and metabolic syndrome (MS) status. Reproduced with permission from Forno et al. (45).*

we can evaluate the association between "genetically determined obesity" and new-onset asthma. MR studies pediatric cohorts have shown that BMI is a "causal risk factor" for asthma, but not vice versa (53-55).

It is of course important to understand that, beyond their genetic predisposition, both asthma and obesity respond to multiple environmental factors and vary along different life stages, and thus it is important to evaluate the role of epigenetic regulation and gene expression in obesity-related asthma (7). Different studies of peripheral blood white blood cells (WBCs) have identified epigenetic and transcriptomic changes in pathways related to immune signaling associated with obesity and asthma, lung function, and other related phenotypes (56, 57). More recently, we reported a transcriptome-wide association study (TWAS) in nasal epithelium that found pronounced differences between obese children with asthma and their peers of healthy weight, with most genes related to interferon and non-T2 signaling pathways (58).

EFFECT MODIFICATION OF OTHER RISK FACTORS

Obesity may modify the effect of air pollution on lung function and asthma morbidity, including fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and second-hand smoke (SHS) (59-62). On the other hand, some studies have reported that air pollution exposure may be linked to higher obesity risk in children (63). There is also recent evidence that obesity may exacerbate

the effects of chronic psychosocial stress, depression, and anxiety on asthma morbidity (**Figure 2**)(64).

MANAGEMENT OF ASTHMA IN OBESITY

The Global Initiative for Asthma (GINA) reports recognize the potential role of obesity in the diagnosis and management of asthma (65). GINA acknowledges that asthma is more common in obese than non-obese people. At the same time, it is important to keep in mind that certain respiratory symptoms seen in obese individuals (for example, dyspnea on exertion) may mimic those of asthma. Therefore, in persons with obesity, it is important to support the diagnosis of asthma with objective measurements of variable airflow limitation that responds to bronchodilators. As part of the assessment of patients with a confirmed diagnosis of asthma, obesity is one of many comorbidities that may affect asthma control, worsen symptoms, and affect quality of life (65). Other comorbidities that affect asthma may also be more frequent in obesity (*e.g.*, obstructive sleep apnea and gastroesophageal reflux disease). While children with obesity and asthma may have reduced response to asthma medications, it is important to note that guidelines still apply, and that ICS and bronchodilators remain the mainstay of asthma therapy in these patients.

GINA and other national guidelines, including those in the US, recommend that clinicians should implement weight reduction strategies in patients with asthma who are obese. GINA specifically recommends this approach as evidence grade B, stating that even a 5%-10% reduction in weight may lead to improvements in asthma outcomes (65). A recent systematic review identified four pediatric randomized controlled trials and concluded that weight loss was associated with improvements in BMI, asthma control, and asthma-related quality of life (66). However, improvements in lung function were less consistent than in adults. As a proof of concept, a recent review bariatric surgery studies in adults concluded that surgical weight loss leads to significant improvements in asthma medication use, hospital admissions, and ED visits (67). Of interest, we reported that improved asthma control was directly associated with improvements in metabolic health, independent of the amount of weight lost after the surgery (68).

CONCLUSIONS AND FUTURE DIRECTIONS

Over the past 2-3 decades, our knowledge of the connections between obesity and asthma has improve substantially. We understand that “obese asthma” is a complex phenotype, with complex pathways that contribute to its pathogenesis and presentation. We also know that not all patients have similar characteristics, and that in some cases even poorly controlled asthma can lead to higher risk of obesity (69). We also understand that weight management and a healthy lifestyle are important components of management of our pediatric patients with asthma and obesity, regardless of their “phenotype”. For readers interested in an in-depth discussion of the immunology and other pathways of obesity-related asthma not covered in this review, recent publications may be of interest (7, 26, 64).

Future studies should focus on: 1) designing pediatric-specific studies that consider important stages of growth and development; 2) improve our ability to endotype/phenotype patients with obese asthma

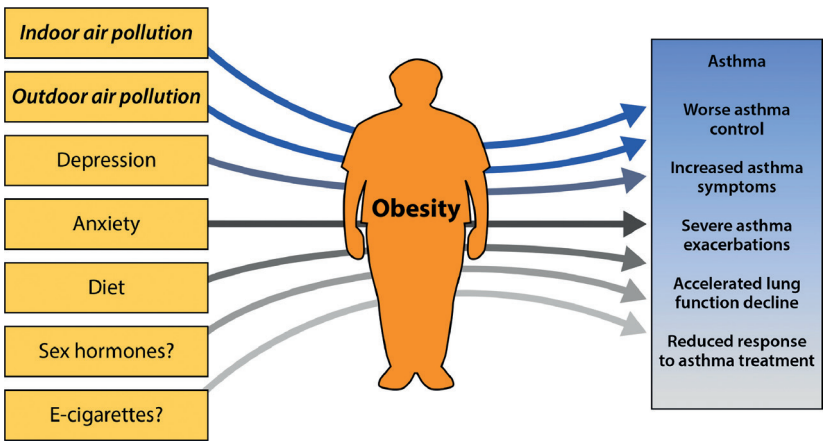

Figure 2. *Potential effect modification by obesity of risk factors that could lead to higher asthma risk or morbidity. Reproduced with permission from Wong et al. (64).*

and develop effective biomarkers; and 3) implement larger, multi-centric trials to test therapeutic targets and interventions that may benefit our patients, using standardized measures and outcomes.

ACKNOWLEDGMENTS

I would like to thank the leadership of the *Italian Pediatric Respiratory Society* and the organizers of the *XXVI Congresso Nazionale* for the invitation and the hospitality, in particular Drs. Fabio Midulla, Enrico Lombardi, Stefania La Grutta, and Salvatore Leonardi.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

Financial support

There were no institutional or private fundings for this article.

Author contributions

Professor Erick Forno is the only Author of this article.

Ethical approval

Human studies and subjects

N/A.

Animal studies

N/A.

Data sharing and data accessibility

The data underlying this article are available in the article.

Publication ethics

Plagiarism

This is a review article and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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