Inhaled Corticosteroid Use in Early Childhood: A Risk for High Body Mass Index?

Epidemiologic studies have repeatedly shown an association between childhood obesity, often measured by a high body mass index (BMI), and asthma morbidity (1). As such, obesity is now recognized as a major risk factor for the development of asthma in children (2). However, in the proverbial chicken versus egg scenario, it is difficult to determine which condition comes first—asthma or obesity—or whether one causes the other. Given the current childhood obesity epidemic in the United States (3), a better understanding of its association with asthma is vital.

Several theories have been proposed to explain how an elevated BMI might lead to airway inflammation and asthma morbidity. The effect of obesity-related systemic inflammatory mediators and circulating oxidants on airway inflammation is considered one of the potential links between obesity and asthma risk in children (2). Obesity-related systemic inflammation has been hypothesized as a priming agent for the lung, leading to exaggerated responses to environmental triggers and subsequent asthma symptoms (4). Recently, systemic IL-6, an obesity-related cytokine, has gained recognition as a potential biomarker for the early signs of metabolic dysfunction in children with asthma and an associated risk of asthma morbidity in both children and adults (5–7). Anti–IL-6 therapy is currently being evaluated as a potential asthma treatment (8, 9). Mechanistically, data suggest that IL-6 is directly linked to airway inflammation (10–12).

But could the reverse be true whereby asthma leads to a higher BMI, and if so, how might this occur? In this issue of the *Journal*, Kunøe and colleagues (pp. 642–650) set out to unravel this long-standing enigma and, in so doing, add novel insight into the use of inhaled corticosteroids (ICS) in early childhood and its potential adverse effect on BMI (13). Through close monitoring of well-characterized children from birth to 6 years enrolled in two independent Copenhagen Prospective Studies on Asthma in Childhood mother-child cohorts (COPSAC2000 and COPSAC2010), the authors demonstrate that ICS use in early childhood is associated with increased BMI at age 6, earlier adiposity rebound, and a statistical trend for increased android body fat percentage. These findings are noteworthy given that this is the first robust prospective observational study evaluating the association of cumulative ICS dose on body fat in early childhood; previous research on ICS use in children has mainly focused on its influence on linear growth and adrenal suppression. The major strengths of this study and design include two large comparable cohorts of young children adhering to similar strict predefined algorithms for asthma diagnosis and treatment at a single clinical research center, detailed record of ICS use and cumulative dose over 6 years, assessment of multiple obesity-related traits, and the ability to adjust for multiple covariates given prospective data collection. Further strengthening the causal pathway of asthma and ICS use to elevated BMI and an innovative element of this study is the consideration of possible obesity heritability in pediatric asthma to address potential confounding; adjusting for a BMI polygenic risk score based on 924,201 SNPs available in 834 children from both cohorts did not attenuate the association of ICS use during the first 6 years of life with higher BMI and earlier age at adiposity rebound.

Although the gold standard for establishing a causal relationship is a randomized controlled trial, it would be difficult to design such a trial including a placebo arm in young children with active asthma. The significant associations reported between cumulative ICS exposure and both elevated BMI at age 6 years and younger age at adiposity rebound did not normalize after stopping ICS treatment and a dose–response effect was not appreciated. Thus, the causality of increased BMI secondary to ICS use in early childhood is not certain despite exemplar prospective observational cohorts such as COPSAC. Nonetheless, this study highlights the lack of existing data on the impact ICS use has in young children, perhaps placing them at higher risk for either being overweight or obese. These same children may then transition into the obese–asthma phenotype associated with greater airflow obstruction and a diminished response to ICS, often resulting in the use of frequent oral corticosteroids leading to even greater obesity, and hence, the beginning of a potential vicious cycle. It begs the question whether young children with moderate severe asthma, especially those with an already elevated BMI, and requiring high ICS doses might be a group better suited for alternative asthma treatments. In addition, the authors did not find a significant correlation between ICS dose during the first 6 years of life and blood lipid outcomes, underscoring the need for identifying predictors of future risk for metabolic syndrome in children with elevated BMI.

The authors concede that the study is limited by a largely white study population, and, therefore, the study findings might not be generalizable to all children. We know that obesity does not affect all children equally, particularly in the United States, where obesity is twice as common in young American Indian and Native Alaskan children with a higher prevalence in Hispanic and African American children than it is in non-Hispanic white and Asian children (14, 15). Furthermore, differences in obesity prevalence among racial and ethnic groups can be seen in children as young as 4 years (16). Factors such as race/ethnicity, culture, and socioeconomics should be considered when weighing the risk–benefit ratio of ICS use in young children susceptible to adiposity for other reasons.

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The findings of this well-designed prospective observational study reveal a potential link between ICS use during early childhood and a risk for elevated BMI. Analyzing BMI trajectory trends in young children on ICS treatment is both important and timely. Obesity-related asthma, the most commonly reported form of pediatric nonatopic asthma, is increasingly being recognized as a distinct asthma phenotype in children. For reasons not fully understood, obese children with asthma are at an increased risk for worse asthma, particularly those with lower socioeconomic status and living in inner-city areas. Kunøe and colleagues have provided the foundation for future studies to be performed albeit in more diverse patient populations to investigate the long-term effects of early ICS use on adiposity from early childhood into adulthood and the underlying mechanisms to explain this connection. ■

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Perdita Permaul, M.D.
Division of Pediatric Pulmonology, Allergy and Immunology
NewYork-Presbyterian/Weill Cornell Medicine
New York, New York
and
Weill Cornell Medical College
Cornell University
New York, New York

Wanda Phipatanakul, M.D., M.S.
Division of Allergy and Immunology
Boston Children's Hospital
Boston, Massachusetts
and
Harvard Medical School
Harvard University
Boston, Massachusetts

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