

Obesity and asthma: The chicken or the egg?

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Asthma and obesity have increased in prevalence over the past 2 decades, reaching epidemic proportions. Obesity is a common comorbidity to asthma and has been associated with not only the development of asthma but also less control of asthma symptoms and increased risk for hospitalization.¹ Recent prospective evidence supports the notion that increased body weight precedes asthma development, but there is ongoing debate as to whether obesity directly increases this risk or whether patients first experience asthma and then become overweight or obese, potentially because of respiratory constraints and reduced physical activity.^{1,2}

Despite a well-established association of obesity with asthma, gaps remain in our understanding of the factors contributing to this relationship. Epidemiologic studies have identified this connection and introduced new concepts but have shed little light in regard to pinpointing the exact mechanisms underlying direct causality. Several biologically plausible interactions have been proposed, including mechanical forces involved in ventilation; chronic systemic inflammation; hormonal influences, including leptin and adiponectin; and additional comorbidities, such as gastroesophageal reflux (GER) and hypertension.^{3,4}

Complicated genetic factors are involved in the development of both obesity and asthma. Interestingly, they even share some of the same candidate pleiotropic genes thought to be involved in the development of both diseases, including genes encoding the β_2 -adrenergic receptor, vitamin D receptor, leptin, protein kinase α , and TNF- α .⁵ Accumulating evidence also supports the complex role of epigenetics and the effect from early-life (including *in utero*) exposures to diet and other environmental factors as a possible common thread linking these diseases.^{6,7}

In addition, little is known or understood in regard to the effect of body mass index on the dose-response relationship to treatment with inhaled corticosteroids, particularly in children. A *post hoc* analysis of the Childhood Asthma Management Program trial identified a decreased response to inhaled corticosteroids in overweight/obese children compared with that seen in normal-weight control subjects in regard to measures of lung function, as well as emergency department visits and hospitalizations for asthma.⁸ Overall, there have been limited studies identifying

unique phenotypic differences for overweight/obese children with asthma, particularly in regard to differences in symptoms and response to therapy. We must exercise caution in extrapolating data from adult populations because their characteristics might differ significantly from those of children.⁴

The article by Lang et al⁹ in this issue of the *Journal* offers a new perspective that identifies differences in symptoms exhibited by overweight/obese children ($\geq 85\%$ body mass index) with asthma compared with lean matched control subjects (20% to 65% body mass index). The authors included children aged 10 to 17 years with a physician's diagnosis of persistent asthma who also had confirmatory objective lung function, methacholine test results, or both. In addition to use of several validated instruments to assess asthma control, symptoms, and quality of life, participants also underwent methacholine challenge testing and measurement of fraction of exhaled nitric oxide values.

Prior research has demonstrated increased airway hyper-responsiveness in both mouse models and human studies for overweight/obese asthmatic patients compared with normal-weight control subjects.³ In addition, mechanical factors, such as decreased functional residual capacity, lower tidal volumes, and small airways more prone to closure, have been hypothesized as potential contributing factors for worse asthma control in overweight/obese asthmatic patients.³ However, Lang et al⁹ did not identify any differences in their overweight/obese children with asthma in regard to objective measures of lung function, including percent predicted FEV₁, percent predicted forced vital capacity, FEV₁/forced vital capacity ratio, or postbronchodilator change in FEV₁. Interestingly, overweight/obese children in this study were less responsive to methacholine challenge, requiring roughly 4 times the dose of methacholine before reaching a significant PC₂₀ value (in milligrams per milliliter). Overweight/obese children also had lower fraction of exhaled nitric oxide values, which is not surprising given the predominantly neutrophilic inflammation associated with obese asthmatic patients in numerous other studies.⁴

Despite the fact that the 2 groups were similar in regard to levels of controller therapy and health care use, overweight/obese children in this study reported 3 times more rescue bronchodilator use per week. In addition, Lang et al⁹ found that overweight/obese children were more likely to identify shortness of breath (odds ratio, 11.8; 95% CI, 1.41-98.7) and less likely to identify cough (odds ratio, 0.26; 95% CI, 0.08-0.82) as their primary symptom associated with loss of control compared with lean children. There were no differences in regard to reported wheeze, chest tightness, or nocturnal symptoms. These findings are in contrast with prior research, which has mostly focused on and/or identified wheeze as the symptom most commonly associated with overweight/obese children.¹⁰

In their discussion the authors remark on the disparity in rescue medication use and primary symptom of shortness of breath in overweight/obese children despite similar lung function and less T_H2 inflammation/methacholine responsiveness.⁹ They also

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identified increased self-report of GER symptoms and snoring (but not obstructive sleep apnea) in the overweight/obese cohort, which is hypothesized as a possible link between these findings.

This study is of importance because of the identification of a unique difference in symptom reporting and higher frequency of rescue medication use between overweight/obese and lean children with asthma, along with a difference in GER symptoms. The authors attempted to differentiate the 2 groups as best as possible by excluding children with intermediate body mass index levels. Limitations include a relatively small number of subjects, particularly in the lean group, and measurement of lung function within a short time interval as opposed to serial measurements over time (all testing occurred within a 3-week time frame from enrollment). In addition, although the frequency of rescue medication use was reported, there was no identification of whether subjects felt relief after using their inhaler. It is possible that overweight/obese children feel short of breath and are conditioned or have been advised to use their rescue medication when this occurs and continue to do so despite lack of benefit. Lastly, GER was characterized by self-report of prior diagnosis, use of acid blockade medications, and subjective symptoms. This study was not designed to identify a causal relationship between obesity, GER, and asthma symptoms, thus prompting the need for additional studies to better determine the connection between these comorbidities in children.

These findings are very intriguing in regard to the assessment and management of overweight/obese children with asthma by history alone and further support the use of lung function testing. The National Heart, Lung, and Blood Institute's asthma guidelines recommend a thorough assessment of medication adherence, comorbid conditions, and environmental exposures before increasing therapy in patients with poorly controlled asthma.¹¹ The findings of Lang et al⁹ support these recommendations, specifically before automatically stepping up controller therapy in overweight/obese patients who report frequent symptoms or rescue medication use. In addition, many overweight/obese children with asthma might even be able to

step down their level of controller medication, particularly if symptoms are deemed to be due to other causes that can be better addressed through non-asthma-related interventions.

In this age of personalized medicine, the importance of characterizing asthma phenotypes and endotypes has emerged as a path to try and provide the highest-quality care to our patients. Although the association between obesity and asthma is very clear, many questions remain in regard to causes, optimal therapy, and prevention. Future studies designed to assess pathophysiologic differences in overweight/obese children with asthma will provide further insight to ultimately develop best practices through targeted therapeutic interventions.

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