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Medical News & Perspectives**Studies Probe Links Between Childhood Asthma and Obesity**

Tracy Hampton, PhD

For decades, investigators have been documenting associations between obesity and asthma in adults, although the underlying mechanisms involved have remained largely unknown. Ongoing work is revealing a link in children as well and is providing new insights into the potential basis of the association.

"There appear to be causative links from the perspective of obesity preceding asthma, but it does not appear to be a simple causal pathway," said Deepa Rastogi, MBBS, MS, director of the Pediatric Asthma Center of the Children's Hospital at Montefiore/Albert Einstein College of Medicine in New York City.

Obesity and the Airways

An estimated 9.3% of US children and 8.0% of US adults have asthma (<http://1.usa.gov/1hm6hkj>), and many adults with asthma developed it when they were children. Also, approximately 17% of children and 36% of adults in the country are obese (<http://1.usa.gov/1e9U3uZ>). Both obesity and asthma disproportionately affect certain minority groups and inner-city residents. Similar to studies conducted in adults, prospective analyses of school-aged groups show that asthma prevalence and incidence increase with the presence of obesity (Boulet LP. *Clin Exp Allergy*. 2013;43[1]:8-21). And when lean and obese nonasthmatic individuals are followed up, those who are obese are almost always found to be at higher risk of developing asthma.

Some research indicates that children with asthma experience incremental increases in body mass index (BMI) for every year after being diagnosed, while adults with later-onset asthma do not undergo significant linear changes in BMI with the dura-



Although a causative link between obesity and asthma has not been established, obesity is known to complicate asthma management.

tion of their condition. This may imply that in early-onset asthma, breathing difficulties may exert effects that lead to weight gain, while in late-onset asthma, obesity may have more of a causative effect on asthma (Holguin F et al. *J Allergy Clin Immunol*. 2011; 127[6]:1486-93.e2). However, there are no convincing data that asthma can cause obesity, while there is sufficient evidence that obesity precedes and is a risk factor for new-onset asthma (Lang JE. *Paediatr Drugs*. doi: 10.1007/s40272-014-0069-1 [published online March 7, 2014]).

Although it's uncertain whether obesity can directly trigger asthma, experts say it's obvious that it can complicate asthma management. "Studies have shown that children with asthma have higher BMIs than those without asthma, and among those with asthma, obese children are more symptomatic, have higher odds of visiting the

emergency department or getting hospitalized," said Rastogi. They also are less responsive to currently available asthma medications compared with normal-weight children with asthma, he said.

Rastogi's work has shown that even small amounts of excess weight may adversely affect lung function in Hispanic and African-American children, who have a higher prevalence of asthma compared with their white counterparts (Vo P et al. *J Asthma*. 2013;50[1]:56-63). The study found that more African American and Hispanic individuals were overweight and obese than white individuals, and that compared with their normal-weight counterparts, lung function was lower in both overweight and obese African Americans and Hispanics, while in whites, it was lower only in those who were obese (not overweight).

Obesity's effect on asthma also may differ with sex. "It is very clear that obesity leading to late-onset nonallergic asthma is more prevalent in adult women compared with adult men, but this female predominance is not present in young children," said Jason Lang, MD, MPH, who is the director of the Nemours Asthma Center and an associate professor at the University of Central Florida College of Medicine, in Orlando. "Several large, very methodologically sound prospective cohort studies in children have not seen a consistently higher risk in females."

Lang added that the increased risk in females seems to start shortly after puberty. The Tucson Children's Respiratory Study showed that girls who became obese were more likely to develop asthmalike symptoms as adolescents, suggesting a potential role for female hormones or sex differences in fat distribution (Castro-Rodríguez JA et al. *Am J Respir Crit Care Med*. 2001;

163[6]:1344-1349; Guerra S. *Am J Respir Crit Care Med*. 2004;170[1]:78-85). In a population of adolescents in the Asthma Adiposity Study, there was a significant relationship between increases in percent body fat and increases in both asthma symptoms and asthma exacerbations in females but not males, which suggests the potential importance of measurements of adiposity other than BMI (Kattan M. *J Allergy Clin Immunol*. 2010;125[3]:584-592).

Mechanistic Links

Although the mechanisms that link obesity and asthma may differ by age, sex, and race/ethnicity, studies point to a common role for inflammation, with obesity-related hormones exerting proinflammatory effects that lead to airway hyperreactivity, a cardinal feature of asthma.

"We know that with obesity come higher levels of circulating 'adipokines' like leptin and TNF- α ; leptin has been shown to penetrate the lung and contribute to alterations in inflammatory cells in the airways," said Lang. A recent study in mice also showed that obesity stimulates production of the cytokine interleukin-17 by innate lymphoid cells in the lung (Kim HY et al. *Nat Med*. 2014;20[1]:54-61).

Obesity can also alter pulmonary mechanics by constricting lung expansion and causing a physical narrowing of the airways (Brashier B, Salvi S. *J Allergy [Cairo]*. 2013;2013:198068). "Breathing at

TNF- α , lymphotoxin- α , vitamin D receptor, and protein kinase C- α (Lang JE. *Pediatr Allergy Immunol Pulmonol*. 2012;25[2]:64-75).

"Each of these mechanisms has supportive evidence and likely plays at least a partial role," said Lang.

Breaking a Vicious Cycle

Although obesity has been associated with more frequent and severe asthma symptoms and the need for increased doses of medication, losing weight can be difficult for children and adults with asthma. "The link between asthma and obesity represents an interplay of factors that can create a vicious cycle," said Lisa Cicutto, PhD, RN, who specializes in asthma management at National Jewish Health and the University of Colorado, Denver. In children, physical activity is important for proper development, socialization, and overall health, but a fear of inducing asthma symptoms may cause a child to limit daily physical activity. This leads to poor cardiopulmonary performance and conditioning, which in turn makes exercise less enjoyable. And of course, regularly restricting physical activity can contribute to weight gain, which itself makes it more difficult to control asthma symptoms.

Despite the hurdles, losing weight has been shown to provide real benefits to both adults and children with asthma. Many studies in adults have demonstrated that losing weight through diet, surgery, or pharmacologic interventions brings improvements in asthma control (Boulet LP. *Clin Exp Allergy*. 2013;43[1]:8-21; Sutherland ER. *Ann N Y Acad Sci*. doi:10.1111/nyas.12357 [published online February 12, 2014]). "And in obese children with asthma, diet-induced weight loss can lead to reduced frequency of symptoms and the need for quick-acting bronchodilators, as well as improved lung function," said Cicutto.

Because obese or overweight children with asthma experience the same general cardiac and mental health benefits from exercise as those without asthma, and because they also experience fewer

asthma symptoms, better asthma control, and higher quality of life through weight loss, efforts are needed to encourage physical activity at an early age, Cicutto said. "The notion that children and youth with asthma can avoid or should avoid physical activity must be rejected," she said. "Approximately 20% of Olympians have asthma, and physical training is possible and safe."

While exercise capacity is primarily associated with pulmonary function among normal-weight adolescents, it was associated with adiposity among obese adolescents in a study by Rastogi and her colleagues, regardless of the presence or absence of asthma (Rastogi D et al. *Pediatr Pulmonol*. 2012;47[11]:1061-1069). "We need to set the bar high for the parents and health care providers to achieve good asthma control with appropriate use of medications and avoidance of known triggers to ensure that all children with asthma are physically active," Rastogi said. Discussions between doctors and parents are crucial because parental concerns can unnecessarily prevent asthmatic children from participating in physical activities (Lang DM et al. *Pediatrics*. 2004;113[4]:e341-e346).

Cicutto explained that children with asthma should be physically active for at least 1 hour each day, like other children in the general population. To accomplish this, they may need medical guidance to gain and maintain asthma control through appropriate use of asthma medications and regular asthma care visits. "If the child or youth is fearful of physical activity or struggling with physical activity, many health centers have childhood exercise programs to work with kids to learn the skills to manage their asthma with exercise and to build the confidence to be full participants in physical activity," Cicutto said.

Lang added that gradual increases in exercise may lead to improved lung function and asthma control over time, even aside from any changes in body weight. And while he stressed the need to continue to investigate the precise pathways that cause altered airway inflammation and other asthma-related effects in obese children and adults, he noted that "based on our current understanding, it is very likely that intervening with the adoption of a healthy diet and establishing a normal body habitus is likely to result in normal airway function and improved asthma." ■

"The link between asthma and obesity represents an interplay of factors that can create a vicious cycle."—Lisa Cicutto, PhD, RN.

lower lung volumes is associated with reduced stretching of the smooth muscle that wraps around the airways, which may make the airway dysfunctional and more responsive to asthma triggers," explained Lang. He also noted that obesity and asthma may have so-called shared origins that include both common genetic markers and dietary components. Researchers have identified several genes with variants associated with both obesity and asthma, including the genes that encode the β 2-adrenergic receptor,