

Metabolic Asthma

Is There a Link Between Obesity, Diabetes, and Asthma?



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KEYWORDS

• Body mass index • Fetal programming • Lung development • Metabolic syndrome

KEY POINTS

- Regardless of body mass index percentile, children diagnosed with asthma are more likely to have higher triglyceride and insulin blood levels than children without asthma.
- Dyslipidemia and hyperinsulinemia, known silent precursors to cardiovascular disease, are also associated with the development of asthma, and confound its epidemiologic link to obesity.
- Diet and physical exercise may influence the development and persistence of innate and adaptive immune mechanisms involved in the pathogenesis of asthma in children.
- Prenatal events, such as intrauterine exposure to imbalanced maternal nutrition, may cause a shift in the trajectory of structural and functional airway development toward a hyperreactive phenotype.
- Monitoring and dietary/pharmacologic control of triglyceride and glucose metabolism during pregnancy and in the first years of life may become an important component of the prevention and management of asthma.

Childhood obesity has reached epidemic proportions worldwide, prompting First Lady Michelle Obama to launch the “Let’s Move!” campaign against childhood obesity in February 2010.¹ Overweight is currently defined as a body mass index (BMI; calculated as the weight in kilograms divided by the height meters squared) from the 85th up to the 95th percentile for age, whereas obesity is defined as a BMI at or greater than the 95th percentile (Fig. 1).² Data from the Centers for Disease Control and Prevention (CDC) indicate that nearly 1 in 3 children in America are overweight or obese and that the rate of obesity already exceeds 30% in the United States.³

What is especially concerning is the rate at which this problem is growing. During the past 3 decades, childhood obesity rates in America have tripled.⁴ Furthermore,

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BMI= Weight/Height²	<ul style="list-style-type: none"> • Reliable indicator of overweight and obesity • Easily obtained • Strongly correlated with body fat percentage
• Underweight	BMI <5%
• Normal weight	BMI 5%-84%
• Overweight	BMI 85%-94%
• Obese	BMI 95%-99%
• Morbid obesity	BMI >99%

Fig. 1. Body mass index.

numbers are even higher among African-Americans and Hispanics, with nearly 40% of these children overweight or obese. If this trend does not change, estimates show that one-third of all children born in 2000 or later will at some point in their lives have comorbidities typically linked to excessive weight. In particular, the prevalence of metabolic syndrome has increased significantly, and more than 2 million children in the United States currently have this condition, defined by systemic hypertension, atherogenic dyslipidemia, and glucose intolerance.

OBESITY-ASTHMA LINK

A similar epidemiologic pattern has been observed for chronic respiratory diseases, particularly asthma. Four million children younger than 14 years have been diagnosed with asthma in the United States,⁵ and the current global estimates of asthma prevalence range from less than 5% to more than 25%.⁶ The parallel increase in obesity and asthma rates among children has led many investigators to postulate a relationship between these conditions,⁷⁻¹⁰ although whether this relationship is causal or confounded by other factors remains a matter of debate.

Previous studies of the association between asthma and obesity have focused on 3 hypothetical mechanisms. The most simplistic theory is centered on specific nutrients, such as antioxidants and saturated fat,⁷ and their role in oxidative lung damage or decreasing the lung's defenses against attacks from biological or chemical agents. The recent emphasis on the potential role of vitamin D deficiency in the pathophysiology of several chronic diseases driven by immunologic or autoimmune mechanisms, including asthma, has given new life to this idea, but the conclusions from interventional trials with high-dose vitamin D supplementation remain controversial.¹¹

A second theory is centered on the mechanical effects of abdominal fat on respiratory system resistance and compliance.^{8,9} Obesity reduces total lung capacity (TLC), particularly through decreasing the expiratory reserve volume and consequently the functional residual capacity. This process leads to the rapid, shallow breathing pattern that occurs close to closing volume in obese subjects. Perhaps more importantly, breathing at low TLC is associated with reduced peripheral airway diameter, and this in turn alters the bronchial smooth muscle structure and function, leading to airway hyperresponsiveness.

The third theory, which is also the most recent and probably most widely accepted, is based on the inflammatory mechanisms implicated in both conditions.^{8,12} In obesity, visceral adiposity is associated with increased expression of multiple soluble mediators that amplify and propagate inflammation locally and systemically. This function involves the recruitment of inflammatory cells by chemokines, such as monocyte chemoattractant protein-1, and the direct synthesis of predominantly

proinflammatory cytokines and chemokines, such as leptin, interleukin 6, tumor necrosis factor α , transforming growth factor β 1, and eotaxin. The resulting perturbation of the balance between Th1 and Th2 immunomodulatory pathways, favoring the latter, has been hypothesized to be one of the mechanisms through which obesity might increase asthma risk or modify asthma phenotype.

DIABETES-ASTHMA LINK

In addition to the hypothetical relationship between obesity and asthma, strong evidence suggests that obesity is associated with the development of insulin resistance and type II diabetes.¹³ In turn, diabetes and insulin resistance are associated with diminished lung function,^{14–16} and some studies have also found a relationship between insulin resistance and lung function among people without diabetes, even after controlling for BMI (Fig. 2).

Therefore, increasing rates of pediatric asthma could result directly from peripheral tissue insulin resistance and compensatory hyperinsulinemia, which interfere with the anti-inflammatory effects of insulin while increasing bronchial reactivity through inhibition of presynaptic M2 muscarinic receptors.¹⁷ In addition, intracellular serine/threonine kinases, such as c-Jun NH₂-terminal kinases, are activated by toll-like receptor signaling in the context of innate immunoinflammatory responses, and also inhibit insulin signaling.¹⁸ Because of the close interdependence between inflammatory and metabolic pathways, pharmacologic ligands of the peroxisome proliferator-activated family of nuclear receptor proteins, widely used to treat hyperlipidemia and diabetes, may also treat the airway inflammation and hyperreactivity characteristic of asthma.

METABOLIC ORIGINS OF ASTHMA

Obesity has generally been thought to be the central hub from which comorbidities such as asthma, cardiovascular disease, and metabolic syndrome originate. Because of this bias, most of the studies designed to examine the interactions between childhood asthma and obesity were based on select cohorts of obese children.¹⁹ A few years ago, the approved authors reasoned that new and important information could result from studies investigating larger, more heterogeneous samples of children stratified by body mass.¹⁹

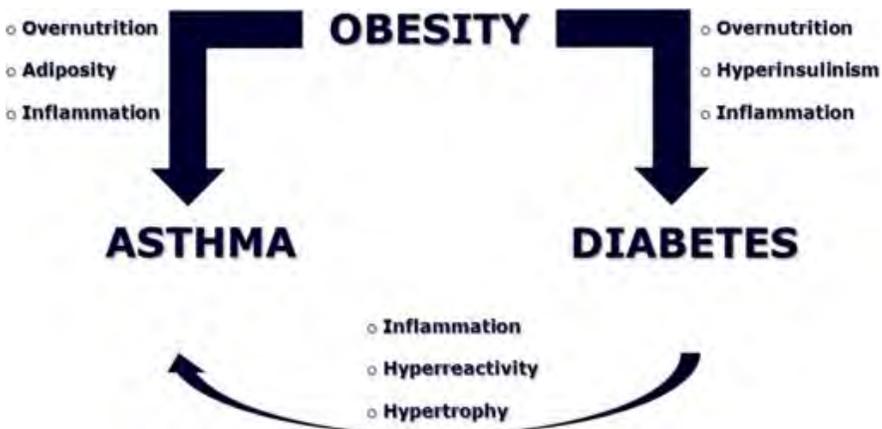


Fig. 2. Obesity-diabetes-asthma link.

A unique opportunity to fill this knowledge gap became available through collaboration with the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project, a federally and state-funded, community-based cardiovascular risk detection program offered to all children enrolled in kindergarten and second and fifth grades in West Virginia.^{20,21} Every year, this project screens tens of thousands of children for BMI. The screening staff also explores the base of the child's neck and axilla for evidence of acanthosis nigricans (**Fig. 3**), a hyperpigmented skin rash associated with insulin resistance and hyperinsulinemia in children,²² and a blood sample is drawn from fifth grade students only to obtain a fasting lipid profile. Before screening, parents or guardians of all participating children provide demographic and family history information by completing a questionnaire.

Analysis of almost 18,000 children enrolled during the academic year 2007–2008 provided the first conclusive evidence of the relationship between asthma and body mass in a large population of children across the entire range of weight percentile categories.¹⁹ This analysis confirmed that asthma prevalence increases with BMI, but only when BMI reaches the obese and morbidly obese range, whereas no difference is seen in asthma prevalence among overweight versus normal weight children (**Fig. 4**). This observation suggests the existence of a threshold beyond which the metabolic derangement begins to affect airway function. Importantly, this study showed similar results in both genders, whereas a previous study in a much smaller sample suggested that body mass may affect asthma prevalence only in girls.²³

The most important conclusion of the present study is that asthma is directly associated with elevated serum triglyceride levels and insulin resistance, regardless of BMI. This finding contributes to the mounting concern about a potentially large population of children, occasionally referred to as being “thin-fat,” who are metabolically obese despite having a deceptively normal weight. These children are at risk of being overlooked because they have a healthy appearance based on weight and adiposity, yet their metabolism is already abnormal and is predisposing them to the same cardiovascular and respiratory comorbidities typically seen in their overweight peers.

Another indirect implication of the present data is that the widely reported association between asthma and obesity may have been confounded by the coexistence of hypertriglyceridemia and insulin resistance. Children with physician-diagnosed



Fig. 3. Acanthosis nigricans (AN). This hyperpigmented skin rash is usually found at the base of the neck and axilla and is highly predictive of insulin resistance in adults. Although it is not as well documented in children, recent data indicate that more than 60% of children with AN also have a homeostatic model assessment index of 3 or greater. The homeostatic model assessment index is the current gold standard of insulin resistance and β -cell function based on fasting plasma glucose and insulin levels.

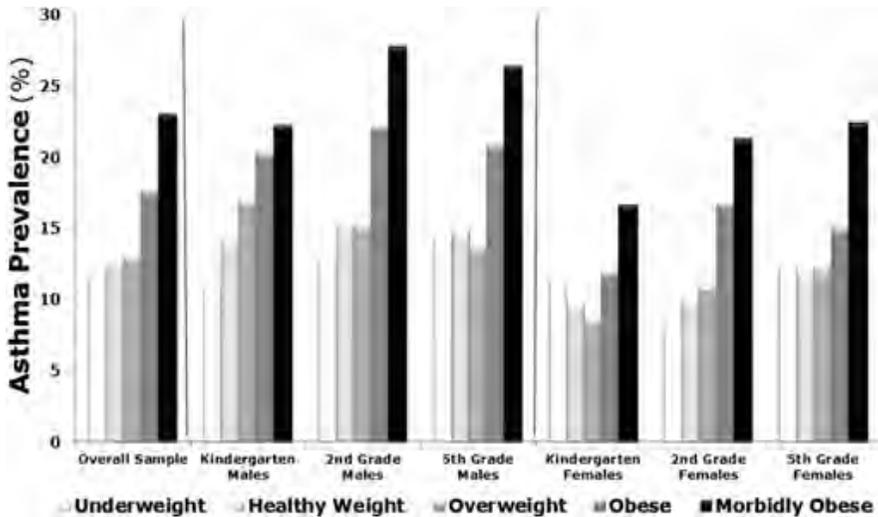


Fig. 4. Asthma prevalence based on weight category. As a general trend, asthma prevalence increases as children's BMI percentile increases. Asthma prevalence in obese and morbidly obese children is significantly higher than in children with a healthy BMI, whereas simple overweight status does not increase this risk. (Adapted from Cottrell L, Neal WA, Ice C, et al. Metabolic abnormalities in children with asthma. *Am J Respir Crit Care Med* 2011;183:443; with permission.)

asthma tend to have higher serum triglyceride levels and higher rates of insulin resistance regardless of their body mass. Thus, dyslipidemia and hyperinsulinemia, which are known silent precursors of cardiovascular disease and diabetes, may also be associated with the development of asthma, and confound its epidemiologic link to obesity.

The present findings imply a strong and direct influence of metabolic pathways on the innate and adaptive immune mechanisms involved in the pathogenesis of asthma in children, and suggest that strict monitoring and dietary/pharmacologic control of triglyceride and glucose levels starting in the first years of life may have an important role in the management of chronic asthma in children.

PRENATAL INFLUENCES

Because metabolic events have been implicated in the pathophysiology of airway inflammation and hyperreactivity, it is conceivable that early-life abnormalities in lipid and/or glucose metabolism contribute to the pathogenesis of asthma in childhood. Increasing evidence suggests that the 9 months spent in the mother's uterus and the first months after birth shape the remainder of a person's life and defines one's medical destiny.

This concept may be true also for the most common respiratory conditions, such as asthma and chronic obstructive pulmonary disease. Preliminary data from the authors' laboratory suggest that an imbalanced diet in pregnancy interferes with lung development and innervation, leading to postnatal airway hyperreactivity independent of the postnatal diet. Furthermore, the prenatal diet can also affect the development of innate and adaptive immune protection, thereby making an infant more susceptible to early-life infections, such as respiratory syncytial virus and human rhinovirus, that predispose to recurrent wheezing and asthma in childhood.

The common belief has been that nothing bad happens to the lungs until the baby is born, except in rare cases of congenital malformations or if gestation is truncated by a preterm delivery, and that the earliest manifestations of lung disease stem from noxious agents attacking the newborn lungs after birth. However, if the maternal diet affects lung development, the understanding of the pathogenesis of respiratory diseases would be completely changed. This notion would turn back the clock of respiratory developmental diseases by months and practitioners would need to start thinking about lung development and disease during pregnancy rather than at birth.

This concept could create a paradigm shift through extending the focus on prevention from the first few years after birth to also include the last few months before birth. The new paradigm is in line with the emerging evidence that many (or most) chronic inflammatory, degenerative, and even neoplastic diseases affecting adults have their origins from often-subtle events occurring during fetal life. The “fetal programming hypothesis” was originally formulated by Dr David Barker more than 2 decades ago to explain the extensively reproduced and confirmed epidemiologic evidence that low birth weight predisposes to cardiovascular disease in late adulthood.²⁴

Barker’s recent death leaves the legacy of this initially controversial but now widely accepted idea that common chronic illnesses such as cancer, cardiovascular disease, and diabetes do not always result from bad genes and an unhealthy adult lifestyle but rather are sometimes caused by poor intrauterine and early postnatal health. In one of his last public speeches, Barker argued, “The next generation does not have to suffer from heart disease or osteoporosis. These diseases are not mandated by the human genome. They barely existed 100 years ago. They are unnecessary diseases. We could prevent them had we the will to do so.”

The authors believe the same concepts can be extended to chronic obstructive airway diseases such as asthma, which is the final product of complex interactions between genetic and environmental variables (Fig. 5). What makes lungs prone to develop chronic disease? Of course, genetic traits inherited from parents are important role. But also the quantity and quality of food the mother eats, the pollution in

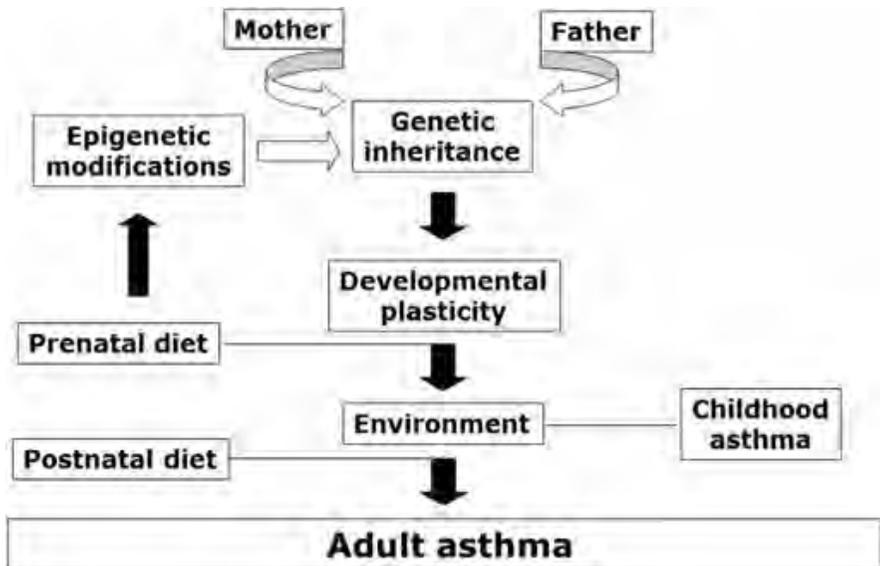


Fig. 5. Fetal programming of asthmatic airways.

the air she breathes, and the infections she sustains during gestation will play a critical role throughout a child's life, perhaps even more important than genetics. In particular, prenatal events such as intrauterine exposure to imbalanced maternal nutrition, infections, or pollutants will cause a shift in the trajectory of structural and functional airway development toward a hyperreactive phenotype. The same intrauterine exposures can affect gene expression via epigenetic modifications, such as DNA methylation and histone acetylation, and by altering the relative expression of regulatory micro-RNAs.²⁵

The resulting neonatal phenotype may predispose the child to aberrant responses to common respiratory infections and airborne irritants, thereby increasing the risk of obstructive lung disease later in life. Postnatal events, such as exposure to indoor and outdoor pollutants and allergens, can further shift the equilibrium of the adult phenotype by exacerbating airway inflammation and hyperreactivity. The continuous range of possible developmental trajectories and multiple sequential events acting during development will define the severity and duration of disease.

Dr Barker believed that public health medicine was failing and that its cornerstone should be the protection of the nutrition of young women. Chronic diseases such as obesity, diabetes, and asthma are becoming epidemic, and their management in adulthood is escalating the costs of health care to proportions unsustainable for any world economy. To successfully control chronic airway diseases that so far have eluded any therapeutic strategy, it is essential to recognize that the months spent in the womb may be the most consequential of a child's life, and to identify the intrauterine and early life events that shape the development of the respiratory system to prevent or redirect dysfunctional phenotypes before they result in actual disease. Ensuring a balanced diet for all pregnant women and their newborns may one day become among the first and most important steps in this direction.

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