

Relationship Between Obesity and Asthma

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The prevalences of both obesity and asthma have clearly increased in recent decades, giving rise to speculation that they may be related. Studies have found that obesity precedes and predicts the onset of asthma (time effect), that increased obesity leads to more severe asthma (dose–response effect), that weight reduction (by diet or gastric bypass) improves asthmatic symptoms, and that obesity co-occurs with intermediate asthma phenotypes (obese young girls undergoing early menarche). In the light of that evidence, we can finally suggest a causal relationship between obesity and asthma. Various biological mechanisms (immunologic and inflammatory, hormonal, genetic, nutritional, mechanical, and others related to physical activity) have been put forth to explain the relationship. However, this relation is complex, involving not only the interaction of genetic and environmental factors in triggering both diseases but also the likely participation of several mechanisms at once.

Key words: *Asthma. Obesity. Overweight. Puberty.*

Camargo et al⁴ carried out one of the first longitudinal studies in adults, showing that women who gained weight after 18 years of age ran a greater risk of developing asthma (incidence) in the next 4 years, regardless of caloric intake or physical activity. Castro-Rodríguez et al,⁵ in the first longitudinal study of a pediatric population, showed that girls, but not boys, who became obese or overweight between 6 and 11 years of age ran a 7-fold greater risk of developing asthma (incidence) than those who maintained normal nutrition and growth, regardless of physical activity or allergic condition. The bronchodilatory reactivity (forced expiratory volume in 1 second) and peak expiratory flow variability were also greater in obese and overweight girls compared to girls with proper nutrition. These findings led the authors to suggest that there may be an anomaly in the regulation of bronchial tone in females (the fourth phenotype of childhood asthma).

In recent years more than 20 epidemiological studies of adults and children have confirmed an association between obesity and the incidence and prevalence of

Relación entre obesidad y asma

Las prevalencias de obesidad y asma se han incrementado ostensiblemente en las últimas décadas, lo que ha llevado a postular que ambas entidades pudiesen estar relacionadas. Si consideramos la existencia de estudios que demuestran que la obesidad precede y predice el desarrollo del asma (efecto de temporalidad), que a mayor grado de obesidad aumenta la gravedad del asma (efecto de dosis-respuesta), que la pérdida de peso (por dieta o derivación gástrica) mejora los síntomas del asma y que la obesidad coexiste con fenotipos intermedios de asma (púberes obesas con menarquia precoz), podemos finalmente plantear que la relación entre obesidad y asma sería de tipo causal. Se postulan varios mecanismos biológicos (inmunoinflamatorios, hormonales, genéticos, dietéticos, mecánicos y actividad física) para explicar esta relación. Sin embargo, esta relación es compleja y además de ser un ejemplo de cómo interactúan los genes y el ambiente en el origen de ambas enfermedades, lo más probable es que exista más de un mecanismo implicado.

Palabras claves: *Asma. Obesidad. Sobrepeso. Pubertad.*

asthma—principally among females—and the relationship is independent of diet, physical activity, or allergic condition. This influence of obesity occurs most often with asthma and airway hyperreactivity, but not other allergic diseases.⁶

Weight reduction (by diet or gastric bypass) has been reported to improve asthmatic symptoms.^{7,8} Therefore, if obesity precedes and predicts the onset of asthma (time effect), and not the reverse, as these studies indicate; if greater obesity means a correspondingly greater effect on asthma (dose–response effect), as other studies have shown; and if there is a relation between obesity and intermediate asthma phenotypes (the fourth phenotype): then a causal relationship can be inferred between obesity and asthma in nonallergic obese girls undergoing early menarche.

However, the obesity–asthma relationship is complex, involving at least 5 possible biological mechanisms:

1. Direct effects on functional respiratory mechanics. The mechanical effects of obesity on the respiratory apparatus seem the easiest to understand. Obesity produces decreased tidal volume and functional residual capacity, both of which reduce the tidal stretch of smooth muscle (the latch hypothesis); thus the ability to respond to natural stress, such as exercise, is hampered by small tidal volumes;

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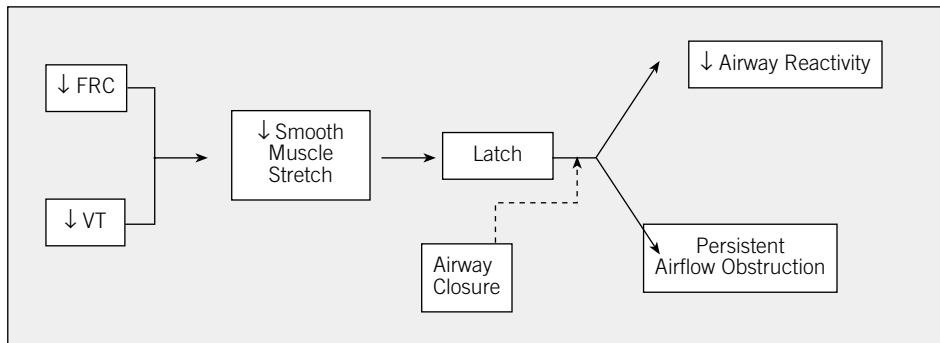


Figure 1. The latch hypothesis. Obesity leads to reduced functional residual capacity (FRC) and tidal volumes (VT), resulting in dynamic decreases in smooth muscle stretch. The resultant latching of the smooth muscle leads to enhanced airway reactivity and irreversibility of obstruction. These effects may be aggravated by breathing around the closing volume, which is characteristic of morbid obesity. (Adapted from Tantisira and Weiss.¹⁰)

consequently, smooth muscle contraction is altered and lung function is impaired. Smooth muscle has an intrinsic cycle of excitation and contraction. In obese people, however, the cycles are shorter, which, compounded with their impaired functional capacity, results in conversion of rapid actin-myosin cycles to slower ones (Figure 1).^{9,10} Still unknown, however, is the dose–response relationship between the amount and/or distribution of body fat and changes in respiratory mechanics.

Another effect of obesity on respiratory mechanics is increased gastroesophageal reflux in obese individuals—including asthmatics, especially adults. Obesity is known to be associated with esophageal sphincter relaxation, resulting in esophageal acid reflux passing into the trachea and airways. The direct contact of gastric acid with the airways causes bronchoconstriction owing to the resulting microaspiration or to the vagal reflex.¹¹

2. Changes in immune and inflammatory responses.

There is ever increasing evidence that obesity is a “proinflammatory” state.¹² Early studies showed an association between obesity and several inflammatory markers: tumor necrosis factor (TNF- α); interleukins (IL), such as IL-6 and IL-1 β ; and C-reactive protein. It has been shown that IL-6 and TNF- α are present in adipocytes and are directly related to total body fat.

In addition, TNF- α is elevated in asthma and is related to the production of T helper (T_H) type 2 cytokines IL-4 and IL-5 and of IL-6 and IL-1 β in the bronchial epithelium. In light of this evidence, it can be inferred that the inflammatory pathway for TNF- α is the same in both obesity and asthma.

Leptin, a *Lep* gene protein, is a hormone produced by adipocytes that acts on the hypothalamus to signal satiety and raise resting metabolism. Leptin plasma levels have been positively correlated with body fat.¹³ It has also been shown that leptin fulfills an important function in stimulating the release of proinflammatory cytokines such as IL-6 and TNF- α by adipocytes. Leptin has also been said to promote a T_H1-type immune response in the form of increased secretion of such proteins as interferon (IFN)- γ ; a relationship between high levels of leptin and IFN- γ has been demonstrated and leptin has been shown to increase expression and secretion of IFN- γ by peripheral-blood mononuclear cells.¹⁴ Furthermore, in malnutrition associated with low leptin levels the T_H1-type response is weaker.¹⁵ Pulmonary hypoplasia was observed in

experimental studies on leptin-deficient mice, indicating a relation between low leptin levels and stunted lung development.¹⁶

However, postnatal effects of leptin on lung development are different: in humans; for example, high plasma levels of leptin are associated with impaired lung function.¹⁷ Furthermore, the effects of leptin can vary according to food intake: in fasting, for example, there are lower levels of leptin in non-obese mice. Leptin also acts on the sympathetic nervous system, specifically by activating the metabolism of brown fat. Both the sympathetic nervous system and brown fat regulate resting metabolism, but the sympathetic nervous system is also crucial in controlling airway tone and diameter—important markers in asthma. Mai et al¹⁸ reported that serum leptin levels were almost twice as high in overweight children diagnosed with asthma as in children with normal nutritional status (Figure 2). Although the difference was not significant—probably due to the small sample size or use of body mass index (BMI) to evaluate obesity—these findings point in the direction of a potential role of leptin that needs confirmation in further studies. Although BMI is the most common parameter used to evaluate obesity, it does not fully correlate with body fat, and at present a combination of BMI and skin fold thickness is being suggested as a better indicator. Finally, there are other hormones associated with obesity (eg, insulin, adiponectin, and neuropeptides) that require further study in the context of asthma.

3. Activation of common genes. We know about genetic pleomorphism, that is, that genes have many effects, for which reason it is biologically possible that genes associated with one disease could also be associated with another. In fact, specific regions of the human genome (such as chromosomes 5q, 6, 11q13, and 12q) have been identified as related to both asthma and obesity.¹⁰

Chromosome 5q contains genes *ADRB2* and *NR3C1*. *ADRB2*, the gene that codes for the adrenergic β_2 receptor, influences sympathetic nervous system activity and is important in regulating not only airway tone but also resting metabolic rate. *NR3C1*, which codes for the glucocorticoid receptor, participates in the modulation of inflammation in asthma and in obesity.

Chromosome 6 contains the genes that code for the major histocompatibility complex and TNF- α , which, as we have pointed out, influence the immune and inflammatory responses in both asthma and obesity.

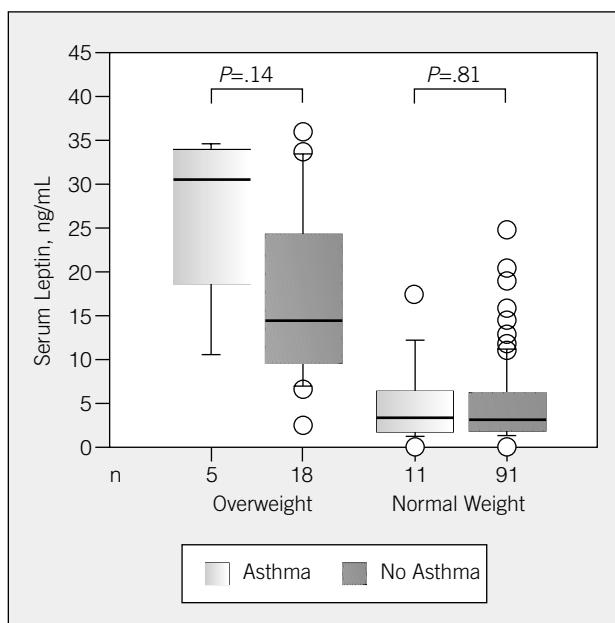


Figure 2. Serum leptin levels in patients with and without asthma, in relation to obesity. (Adapted from Mai et al.¹⁸)

Chromosome 11q13 contains the genes for the uncoupling proteins UCP2 and UCP3, and the low affinity immunoglobulin E receptor. The UCP2 and UCP3 proteins influence resting metabolism, but not in asthma. The low affinity immunoglobulin E receptors, on the other hand, form part of the inflammatory response mediated by T_H cells, which proliferate in asthma but not in obesity. Lastly, chromosome 12q contains genes for inflammatory cytokines associated both with asthma (eg, IFN- γ , LTA4H, nitric oxide synthase-1) and with obesity (eg, STAT6, insulin-like growth factor-1, CD36L1).

4. *The influence of hormones and sex.* It is remarkable that right from the first longitudinal studies the effect of obesity on asthma was observed more often in females than in males.^{4,5} We know that adipose tissue contains the enzyme aromatase, which is responsible for converting androgens into estrogens. Obesity generally increases the production of estrogens, which are associated with early menarche in girls and delayed puberty in boys.^{19,20}

In the Tucson cohort, Castro-Rodríguez et al,⁵ observed the prevalence of asthma to be greater among obese girls with early menarche (before 11 years of age) than among those with a later menarche (Figure 3). This would indicate that obesity alters the production (or peripheral sensitivity) of the hormones associated with puberty in girls and that increased production of female hormones (or their sensitivity) alters lung development and regulation of airway tone in puberty-age girls (by enhancing bronchodilator reactivity, as we pointed have out). This finding was confirmed in a study in adults in France, where Varraso et al²¹ observed that the association between obesity and asthma was more evident among women with early menarche. It has also been reported that the use of exogenous estrogens is a risk factor for a higher incidence

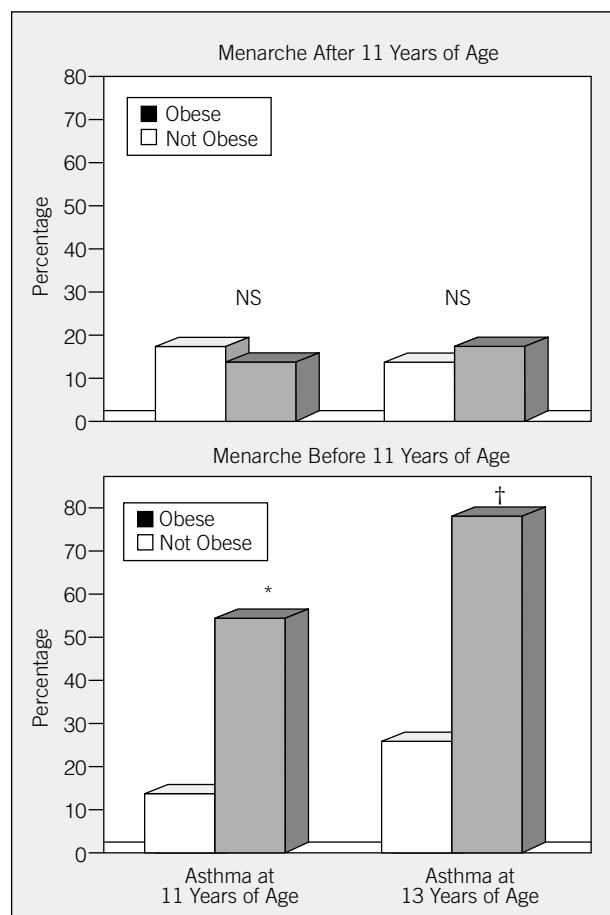


Figure 3. The relation between obesity and asthma in girls with menarche after 11 years of age (top) and girls with early menarche before 11 years of age (bottom). Asterisk indicates $P=.01$; †, $P=.004$; NS, not significant. (Based on data in Castro-Rodríguez.⁵)

of asthma in women.²² The mechanism by which estrogens cause increased airway responsiveness in asthma is still unknown, but in clinical practice cases of women with severe and refractory asthma associated with morbid obesity are not uncommon. Curiously, female sex is also associated with greater severity of irreversible airflow obstruction or chronic obstructive pulmonary disease. However, it is unknown whether resistance to inhaled corticosteroids in cases of severe asthma is associated with the metabolic effects of asthma, increased inflammation, or estrogenic effects. Guerra et al²³ recently reported that overweight and obesity at 11 years of age and early menarche in the Tucson cohort were both risk factors for persistent wheezing after puberty (Figure 4).

5. *The influence of diet, physical activity, and "fetal programming."* Diet and physical activity are 2 factors that influence obesity and, apparently, asthma. It has been postulated that factors at work in pregnant women may also effect the development of fetuses by affecting birth weight and genetic programming. Such *in utero* events would have a repercussion on the subsequent onset of asthma and obesity. The soundness of this hypothesis is based on the recognition that most cases of asthma

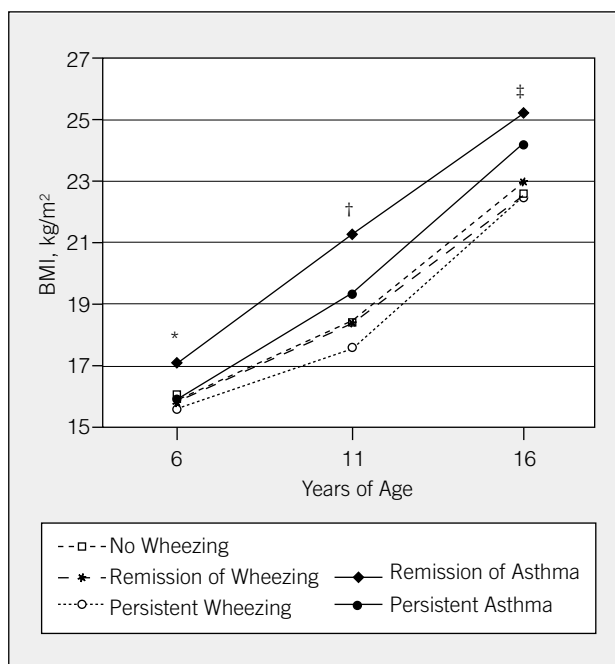


Figure 4. Obesity as a risk factor for persistent wheezing from 6 to 16 years of age. Asterisk indicates $P=0.001$; †, $P=0.0001$; ‡, $P=0.004$. (Adapted from Guerra et al.²³)

occur early in childhood, before the age of 6 years, and that much of what happens later in life is only a worsening of childhood conditions. While prospective studies have been unable to demonstrate that physical activity influences the obesity–asthma relationship, the physical activity of pregnant women may be important in the *in utero* development of the sympathetic nervous system. The sympathetic nervous system is the prime regulator of the activation of brown fat, which in turn is the main regulator of thermogenesis and resting metabolic rate via the uncoupling proteins. In addition, we know that the 3 types of β -adrenergic receptors are expressed in adipose tissue.

Furthermore, a variety of dietary factors have been reported as being associated with the prevalence of asthma in adults and children. For example, the antioxidants (vitamins C and E), carotene, riboflavin, and pyridoxine may play an important role in enhancing immune system activity, reducing symptoms of asthma and eczema, and improving lung function. Romieu et al²⁴ recently showed that adult women who ate fruits and vegetables (tomatoes, carrots, and leafy green vegetables) had a lower prevalence of asthma. Likewise, the increased consumption of trans fatty acid in the pediatric population is associated with a reduction in the prevalence of asthma.²⁵ However, it should be emphasized that many of the studies on diet and asthma are carried out on persons already diagnosed with asthma. It is unknown whether the diets of pregnant women influence the onset of obesity in their offspring, but it is interesting to note that the relationship between birth weight (regardless of gestational age) and the risk of asthma follows a U-curve: both low and high birth weights carry a greater risk of asthma.^{26,27} A U-curve has also been used

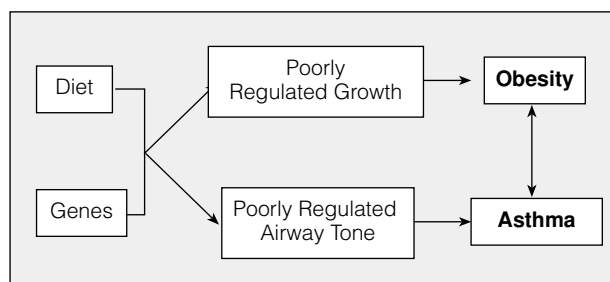


Figure 5. The interrelation of genetic and environmental mechanisms underlying the obesity–asthma relationship.

to describe the relationship of low and high BMI with increased bronchial hyperreactivity in males.²⁸ This suggests that fetal programming could affect the subsequent onset of obesity and asthma.

The complex interrelationship between obesity and asthma is an example of how genes and environment interact in 2 entities, and more than biological mechanisms are likely to be involved. Through inflammatory mechanisms or lifestyle changes, obesity may give rise to asthmatic symptoms in susceptible individuals. The interaction between diet and genes may cause abnormalities in body growth patterns (leading to obesity) and/or alter airway tone (triggering asthma), and multiple interrelations between obesity and asthma may then take place (Figure 5).

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