REVIEW ARTICLE

Relationship among obesity, asthma and pulmonary function

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ABSTRACT

Obesity and asthma are public health issues. Many studies have demonstrated a relation between both conditions. There is a positive correlation between body mass index and asthma; the risk of suffering from asthma is greater as body mass increases. The probability for developing asthma in an obese school-age child may be as high as 50%. An association between obesity and asthma has been described more frequently in females, particularly in adult surveys. Obesity may directly affect asthma phenotype by mechanical effects in the respiratory tract, gastroesophageal reflux, production of proinflammatory cytokines in fat tissue (interleukin 6, tumor necrosis factor, leptin, adiponectin), activation of common genes, or by increased estrogen production. Obesity may worsen asthma symptoms as well as causing poor control of the condition. Weight loss improves symptomatology and pulmonary function, along with reducing the use of antiasthmatic medication. Therefore, it is necessary that management of obese asthmatic patients includes a weight control program.
Key words: obesity, asthma, body mass index, phenotype.

INTRODUCTION

In recent decades, asthma and obesity have increased markedly in many countries.[1,2] This situation represents a public health problem due to the probability of an early death in a large number of individuals.[3,4] The World Health Organization (WHO) includes both conditions among the principal chronic diseases.[5,6]

Obesity

Obesity is the excess of accumulated fat that affects health.[7] The fundamental cause is an imbalance between intake and expenditure of energy. It is closely linked to a Western lifestyle where there is a decrease in physical activity and an inadequate diet.[8] According to the 2006 National Survey of Health and Nutrition (ENSANUT), the criteria of the International Obesity Task Force (IOTF)[9] in the group of 12- to 18-year-olds showed that males had a prevalence of overweight of 21.2% and obesity of 10.0% and females had a prevalence of 23.3% and 9.2% respectively.[4]

In general, according to the 2006 ENSANUT, 70% of adults in Mexico are overweight or obese, whereas for teens in the metropolitan area, obesity and overweight are present in 28% of males and 30% of females 10 to 17 years of age.[4] Although there was no significant change for the latter age group with regard to the report of the 2000 ENSANUT,[10] the prevalence is high and this is concerning because obesity and overweight are associated with the development of pulmonary, orthopedic, gastroenterological, and neurological conditions, insulin resistance, dyslipidemia, hypertension and type 2 diabetes mellitus (T2DM) (Figure 1).[11,13]

To establish the diagnosis of overweight and obesity in clinical practice, one of the most accessible and practical indexes to estimate excess fat is the body mass index (BMI), which is the value of weight (in kg) divided by the value of height (meters) squared.

The expert committee for the assessment, prevention and treatment of children and adolescents with overweight and obesity problems recommended a calculation of BMI in children 2 to 18 years of age.[7] Overweight is defined as

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the value of BMI ≥85th percentile and obesity when it is ≥95 percentile for age and gender [based on the Centers for Disease Control and Prevention (CDC) percentile charts],[14] whereas morbid obesity is established when the BMI percentile is ≥99 or, in adolescents, when there is a BMI ≥35 kg/m^2. This cutoff value was defined based on the Bogalusa cohort, which identified subjects with high risk of major biochemical abnormalities associated with the early development of diabetes, cardiovascular disease and severe adult obesity.[12,14] These have been observed, in an early form, in slippage manifestations of the femoral head (10%), fatty liver (30%), metabolic syndrome (MetS) (35%), sleep disorder breathing (70%) and a high frequency of insulin resistance.[15,16]

Asthma

Asthma is a chronic inflammatory disorder of the airways involving many cells and elements (adipose, eosinophils, neutrophils, lymphocytes, macrophages, and epithelial cells) that cause recurrent episodes of nocturnal predominance cough, wheezing, difficulty breathing and a sensation of chest tightness. These symptoms are usually associated with a large but variable bronchial obstruction, which is often reversible either spontaneously or with treatment.[17] In relation to asthma in children, the prevalence varies widely worldwide, even in our country, for example in Merida, Tabasco and Ciudad Victoria, it is presented in a high percentage of students (12%), whereas in the northern area of the Federal District of Mexico City it occurs in 9.9% of adolescents and 8.5% of school children.[18,19] Our goal in this review is to show the main features of obesity and asthma and the causal relationship between the two.

Relationship Between Asthma and Obesity

The parallel increase in the prevalence of asthma and obesity in several regions has led to the assumption that both entities have a causal relationship.[20-22] Although this relationship is not entirely clear, probably because of the complexity of the epidemic, both diseases have chronic inflammatory processes in common.

It has been reported that obesity increases the incidence of asthma in adults.[23-38] However, there is a great heterogeneity in the magnitude and importance of this relationship as there are differences in the duration of follow-up visits, number of patients, distribution by gender and age and

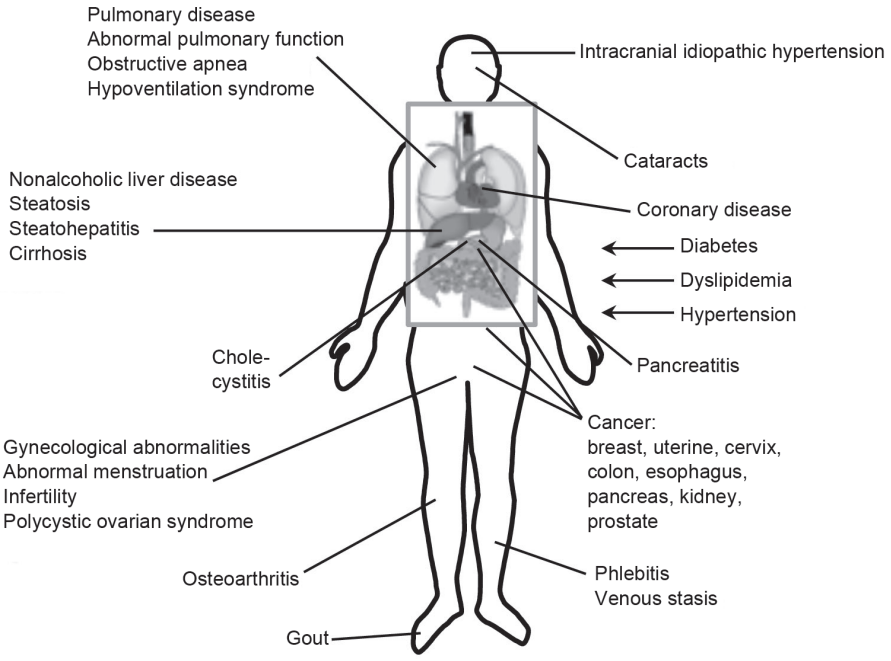

Figure 1. Complications of obesity.

the BMI, in addition to other variables that could explain differences in exact estimates.[28,39] For example, obesity in postpubertal females precedes asthma and it has been shown that the relationship between obesity and asthma is significant; however, some studies have found that this relationship is similar for both genders.[40,41] In others, however, this situation occurs only in males.[42]

Several cross-sectional studies found an increased prevalence of asthma in obese patients,[22] although to have a better detection of the effects of obesity on the development of asthma, prospective studies have been of greater value.[43] Since 2000, with a better design of studies, we have shown an increased risk in obese patients, ranging from 1.1 to 3 times, to develop asthma.[24,40,44,45]

After locating 2006 references in the literature, Beuther and Sutherland performed a meta-analysis of only seven studies that met the inclusion criteria. Eutrophic, overweight and obese adults were evaluated for the development of asthma (n = 333,102). When comparing BMI among them, the risk of asthma (OR) was 1.5 (95% CI 1.27-1.80) for those with a higher BMI (BMI >25) with a dose-response effect of BMI on asthma incidence in both males and females.[46] In personnel of the Hospital General of Mexico (HGM), we found a significant association of asthma symptoms in females with a BMI >85% and WC >80 cm.[31]

Studies in the Pediatric Population

Studies that have been conducted in the pediatric population are more heterogeneous both in terms of strength of their results as well as in the direction of asthma-obesity relationship. Gold et al. in 9,828 children between 6 and 14 years of age who were followed for 5 years reported a 2.2 times higher risk for asthma, especially in overweight girls.[47] In another study of 3,792 children, they found that overweight and obesity increased the risk of asthma, more often in boys than in girls.[48] Mannino et al. conducted a study over 14 years on 4,393 children without asthma during their first 2 years of life. They showed that the high BMI group (>85th percentile) had a 2.4 times greater risk of developing asthma than the group with a lower BMI.[49] In the Flaherman and Rutherford meta-analysis that analyzed 12 studies,[50] the authors observed that in four studies there was a four times greater risk for asthma in obese school-age children.[51,52] The effect of birth weight and the development of asthma in 9/12 studies was 1.2 times greater when birth weight was >3800 g.[50] Although other authors have shown that not only the high birth weight (>3500 g) is a risk factor, but also a weight <2500 g.[53] Table 1 summarizes two meta-analyses, one in children and the other in adults, with a risk of 1.5 and 95% CI of 1.2-1.8.[46,50] Contrary to the earlier meta-analysis, there is no effect on a smaller number of studies.[51,52]

The Godfrey and Barker hypothesis suggests that there is fetal programming that can lead to the subsequent development of chronic diseases such as obesity and asthma.[54] The programmed result of a harmful stimulus during a critical period (sensitive) in early fetal development may be reflected in the adult stage.[55]

Among the obese population, there has been a relationship of nonallergic phenotype asthma with more severe symptoms: increased use of anti-asthma medication and poor response to inhaled anti-inflammatory steroids.[56] Another way to assess the relationship between asthma and obesity is the beneficial effect that weight reduction has in reducing symptoms, in medication use and in the number of visits to the emergency room due to crisis.[57,58] In addition, obese patients have a combination of mechanical and inflammatory effects that can cause pulmonary disability.

Lung function tests used for clinical analysis are spirometry and plethysmography. For the first, a spirometer is required that shows a numerical and graphical curve flow/volume and volume/time with expired and inspired air, which determines the volume and the velocity of air that moves from the lungs outward during a forced expiratory maneuver. With this test, the following data are calculated as forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), forced expiratory flow obtained from 25 to 75% of the exhaled vital capacity (FEF 25 to 75%) and the ratio FEV1/FVC% (Tiffeneau index). There are mainly two spirometric patterns, the restrictive and the obstructive. In the restrictive pattern, there is a limitation of the lung expansion that may be caused by alterations of the parenchyma, pleura, chest wall or neuromuscular apparatus. In the obstructive pattern there is an increased resistance to the airflow and the FEV1 and FEV1/FVC% relation are reduced.

Plethysmography is a more sophisticated and costly procedure. The technique is based on the gas laws. In addition to determining the volumes and flows (same as spirometry), it measures lung capacities. Of these, the most clinically useful is the total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV).

Table 1. Results of the meta-analysis in regard to obesity and asthma

Authors	*No. of studies*	*Method*	*Conclusions*
Flaherman and Rutherford[50]	Twelve prospective and retrospective studies in children	Review in Medline from January 1996-October 2004 BMI >85th percentile Ponderal index ≥27 kg/m^2 Birth weight ≥3800 g	Four studies verified that obese children had a RR 1.5 times higher for asthma (95% CI 1.2-1.8) BMI >85th percentile was more prevalent for children with asthma Nine of 12 studies had a RR = 1.2 for asthma in children with a birth weight >3800 g (95% CI 1.1-1.3)
Beuther and Sutherland[46]	Seven prospective studies in adults	Of 2006 references, seven studies were included with BMI 25-29.9 kg/m^2 for overweight, ≥30 kg/m^2 for obesity	For asthma risk, OR was 1.51 with BMI ≥25 kg/m^2 With regard to asthma incidence between normal and overweight subjects, OR was 1.38 (95% CI 1.17-1.62) When comparing obese vs. normal weight, OR was 1.92 for obese subjects (95% CI 1.43-2.59)

RR, relative risk; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index.

Major Changes in Lung Function Caused by Obesity

Obesity can cause respiratory symptoms such as dyspnea from exercise, increased respiratory effort and changes in lung capacity. These may be interpreted as symptoms suggestive of asthma (wheezing) without being asthma. It is necessary to have, through testing of pulmonary challenge, confirmation if there are changes in the bronchial reactivity coupled with chronic respiratory symptoms such as coughing, wheezing and chest tightness.[59]

Obesity presents a tightening of the airways due to a combination of effects on the lungs and the effort of the chest wall for breathing. Lung compliance is reduced and appears to be exponential with respect to BMI.[60] It can also cause an increase of pulmonary blood volume along with alteration of airway closure by the decreased volumes, resulting in small areas of atelectasis or increased alveolar surface tension due to the reduction of FRC.[60]

The large amount of energy needed to move an obese body as well as the decreased distensibility or "compliance" of the chest wall by fat infiltration in the accessory respiratory muscles leads to a subjective sensation of breathlessness. This "battle to breathe" may cause respiratory muscle weakness and decrease the maximum inspiratory pressure compared with nonobese subjects. For these reasons, it is not difficult to understand that, with weak muscles, poor "compliance" or chest wall distensibility and a large body mass, exercise tolerance is poor.[61] In addition, central adiposity increases intra-abdominal pressure, which displaces the diaphragm. This causes a chronic abdominal compartment syndrome resulting in decreased lung volumes and pulmonary dynamics.[60] According to the degree of adiposity, there may or may not be impaired lung function. The respiratory pattern that predominates in obesity is restrictive but can also be mixed (restrictive and obstructive).

Adipose tissue surrounding the chest and abdomen (visceral fat) causes a load on the chest wall and reduces the FRC. This reduction and that of the expiratory reserve volume (ERV) are detectable even with a modest increase in weight.[60]

As for the intensity of the alteration of the airway caliber, there is a slight decrease in lung volumes. Nevertheless, they are rarely found below normal ranges, even in extremely obese patients.[60]

A low FRC increases the risk of expiratory flow limitation and airway closure. The sharp decline of ERV can lead to alterations in ventilation and distribution. Closing of the airways in dependent areas of the lung can cause differences in ventilation perfusion that bring a change in the balance of the pressures of inflation and disinflation of the lung (Figure 2).[60] There is an exponential relationship between BMI and FRC with a reduction of this, even in overweight patients, which can become so pronounced that it is equal to the residual volume.[62] However, the effects of obesity on lung volumes, TLC and RV may be modest.[60]

An association has reported between excessive weight and TLC reduction, although the changes are small. They usually remain above the lower limit of normal, even in severe obesity.[62] RV is usually well preserved and the RV-TLC relation remains normal or slightly higher.[56,62,63]

The reduction of TLC is probably due to the mechanical effect of fat, which reduces the decline of the movement of the diaphragm by abdominal mass increase and limits the scope of the lung to expand during inflation. All this is corrected with weight loss.[60,64]

When there is a small reduction in TLC and a good status of preservation of the RV, FRC reduction is manifested by an increase in inspiratory capacity and a very marked decrease of ERV.[62] With respect to the lung volume, FEV1 and FVC may or may not be affected. If they are altered, the effect is very mild in adults and children[59,65] and the relationship of FEV1/FVC% is usually well preserved or even increased.[65-67] However, today there are controversies that have served to support the fact that obese children may have an obstructive pattern with a decrease of FEV1/FVC%.[68] This draws our attention because it is a common finding in asthma.[69]

Despite the considerations on the modest reduction in lung volumes, there may be a reduction of the airway diameter by peripheral fat infiltration. There will be changes in the airway smooth muscle function with a subsequent loss of coordination in the cycle of actin and myosin crosslinking. This potentially increases the obstruction and alters the response to a stimulus such as exercise or bronchial challenge, key in the diagnosis of bronchial hyperresponsiveness (BHR) (Figure 2).[70]

Among the studies for the development of BHR in obese patients is that of Kaplan and Montana who corroborated BHR in exercise with obese children vs. healthy children.[71] Similarly, Gennuso et al. described a higher frequency of BHR in asthmatic obese patients vs. nonobese asthmatic patients.[72] In the Respiratory Health Survey of the European Community, an increase was observed in BHR in obese males[73] and in a longitudinal study (Normative Aging Study) there was also an association between BMI and BHR with an OR reported of 7.[74] In our experience, in a group of obese children who underwent an exercise challenge test, we observed patterns of BHR similar to those of eutrophic asthmatic children and a greater drop in FEV1 in asthmatic overweight and obese vs. nonobese asthmatics.[75] Reduction in lung volumes with chest wall restriction and increased oxygen consumption by respiration contribute to comorbid conditions such as gastroesophageal reflux and sleep apnea.[76-78]

Obese patients have a sixfold greater risk of developing obstructive sleep apnea. This condition can, in itself, predispose the risk of developing arterial hypertension, cardiovascular disease, behavior disorders, poor school performance and a poor quality of life.

Respiratory Disorders in Obesity

Weight loss has been shown to improve lung function and asthma symptoms, but not necessarily the airflow obstruction or BHR.[79-81] In children, it has been observed that the respiratory limitation of nonmorbid obesity is more related to their perception of being symptomatic than with the worsening of asthma. Similarly, activity levels and maximal aerobic potential are lower.[82]

In a study of asthmatic children who were 3 to 5 years of age, we found an association between the increased BMI with more truancy, more emergency room visits and greater limitation of physical activity.[83]

It has also been noted that in an intensive care unit, asthma attacks were more common in obese children. Along

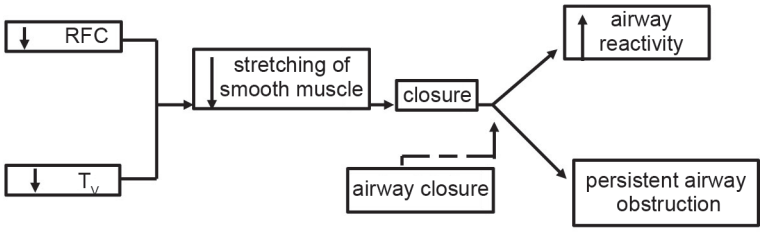

Figure 2. Mechanical effects of obesity in regard to pulmonary function: RFC, residual functional capacity; T_V, tidal volume.

with that, they had a longer hospitalization and required a longer course of supplemental oxygen, continuous albuterol and intravenous steroids.[84]

Influence of Gender and Hormonal Relationship

As mentioned at the beginning of this review, the connection between obesity and asthma has been more favored in postpubertal females than in males, whereas some pediatric studies prove this and others do not.[24,28,31,34,85] In the cohort study by Castro-Rodriguez et al., the authors found that the prevalence of asthma symptoms were greater in obese girls who had an early menarche (before the age of 11 years) than among those who presented it at a later age.[86] One likely explanation is that this is due to estrogen.[87,88] In obesity, there is an increase of the enzyme aromatase, which is in adipose tissue and converts androgens into estrogens. These have a bronchoconstrictor action and are associated with early menarche and with delayed puberty in boys.[88] According to this fact, it has been postulated that obesity alters the production of hormones associated with puberty. An increased production of female hormones (or their sensitivity) alters lung development and regulation of airway tone in pubertal girls. However, this mechanism is not well understood.

Genetic Factors

It is biologically possible that certain genes that are related to a particular disease may be related to other diseases. It has been determined that certain specific regions of the human genome are associated with both asthma and obesity, e.g., the *loci* 5q, 6, 11q13 and 12q (Table 2).[68]

Dietary Influence

It has been reported that diet influences the prevalence of asthma. For example, antioxidants (vitamins C and E), carotene, riboflavin and pyridoxine may have a significant effect in increasing immune function, reducing symptoms of asthma/eczema and improving lung function. Romieu et al. reported that adult females who consumed fruits and vegetables had a lower prevalence of asthma.[89]

Asthma, Obesity and the Environment

The influence of the environment, both inside and outside, as triggers of asthma attacks is well documented.[90] Figures 3 and 4 show the main relationships between asthma, obesity and environmental factors.

Asthma, Obesity and Atopy

There are a variety of factors that can trigger asthma, one of which is mediated by immunoglobulin E (IgE), but this has not been associated with an increased BMI. Although the phenotype of asthma that has been associated with obesity is of a severe type, this most likely appears to be mediated by another mechanism.[91]

Obesity and Mediators of Inflammation

Silent and harmful inflammation that causes obesity may be increased when it coexists with asthma. Increase in the function of adipose tissue in obese subjects leads to a systemic pro-inflammatory state in which serum concentrations of cytokines and soluble fractions in receptors and chemokines are increased.[92] Many of these mediators are synthesized and secreted by adipose tissue cells and have been given the generic name of adipokines. Included in this group are IL-6, IL-10, eotaxin, tumor necrosis factor (TNF), transforming growth factor beta (TGF-β1), CRP, leptin and adiponectin.

TNF is found in adipocytes and is directly related to body fat, increases in asthma and to the production of cytokines T_H2 (IL-4, IL-6) in the bronchial epithelium. Serum levels of IL-6 are elevated in obese subjects and are associated with asthma severity.[93] One of the greatest advances is the knowledge of the signaling pathway of leptin. There are certain inactivating mutations affecting the genes encoding this pathway, which affects a small percentage of the presence of severe, early onset, obesity.[94]

Leptin is produced in adipose tissue and binds to its receptor in the arcuate nucleus. Its concentration increases with increasing fat mass; however, in individuals with low fat mass (e.g., lipodystrophy syndrome or anorexia nervosa), leptin levels are low. Fasting decreases leptin concentration in an acute manner and its deficiency causes a signal that stimulates the search for food, consumptive behavior and energy expenditure. Restoration of normal levels leads to limiting food intake and changes the activation regions involved in appetite control.[94]

Many studies oriented to the relationship between asthma and obesity have focused on the role of leptin because it was believed to act as a lipostat where the amount of fat stored in fat cells increases and is released into the bloodstream. This constitutes a negative feedback signal to the hypothalamus, which responds with the release of anorexigenic peptides and suppresses the production of orexigenic peptides. The energy expenditure increases as

Table 2. Candidate genes with potential relevance for asthma as well as for obesity

Locus	*Candidate genes*	*Relevance for asthma*	*Relevance for obesity*
5q	ADRB2	Control of airway tone	Control of rate of metabolism
	NR3C1	Modulation of inflammation	Modulation of inflammation
6p	TNF, HLA	Immune modulation and inflammatory response	Immune modulation and inflammatory response
11q13	UCP2, UCP3	Unknown	Control of rate of metabolism
12q	IgE (FCεRB)	Th2 inflammatory response	Unknown
	STAT6, IGF1, IL1A, LTA4H	Modulation of immune response	Modulation of inflammation

2AR, beta-2 adrenergic receptor; NR3C1, glucocorticoid receptor; TNF, tumor necrosis factor; HLA, human leukocyte antigen; UCP, uncoupling protein; IgE (FCεRB), low-affinity receptor for immunoglobulin E; STAT6, gene signal transducer and transcription activator; IGF, insulin growth factor; IL1A, interleukin 1-α; LTA4H, leukotriene hydroxylase 4H.

does the basal metabolic rate and body temperature. At the same time, there is an adjustment in the basal equilibrium point for the reduction of lipogenesis and increases the lipolysis in adipose tissue.[95]

Another role of leptin is that it has a considerable structural homology with the long-chain cytokines such as IL-6 and is capable of regulating the proliferation and activation of T-cell lymphocytes, promoting angiogenesis and recruiting monocytes and activated macrophages.[96] It is also important for the normal development of the lungs and acts as a mediator in the differentiation between lipofibroblasts and fibroblasts and the synthesis of pulmonary surfactant.[97] Unlike other adipokines, adiponectin serum levels are reduced in obese subjects and more so in obese asthmatic patients.[98] It has been shown that this hormone has anti-inflammatory properties, even in the airways.[99]

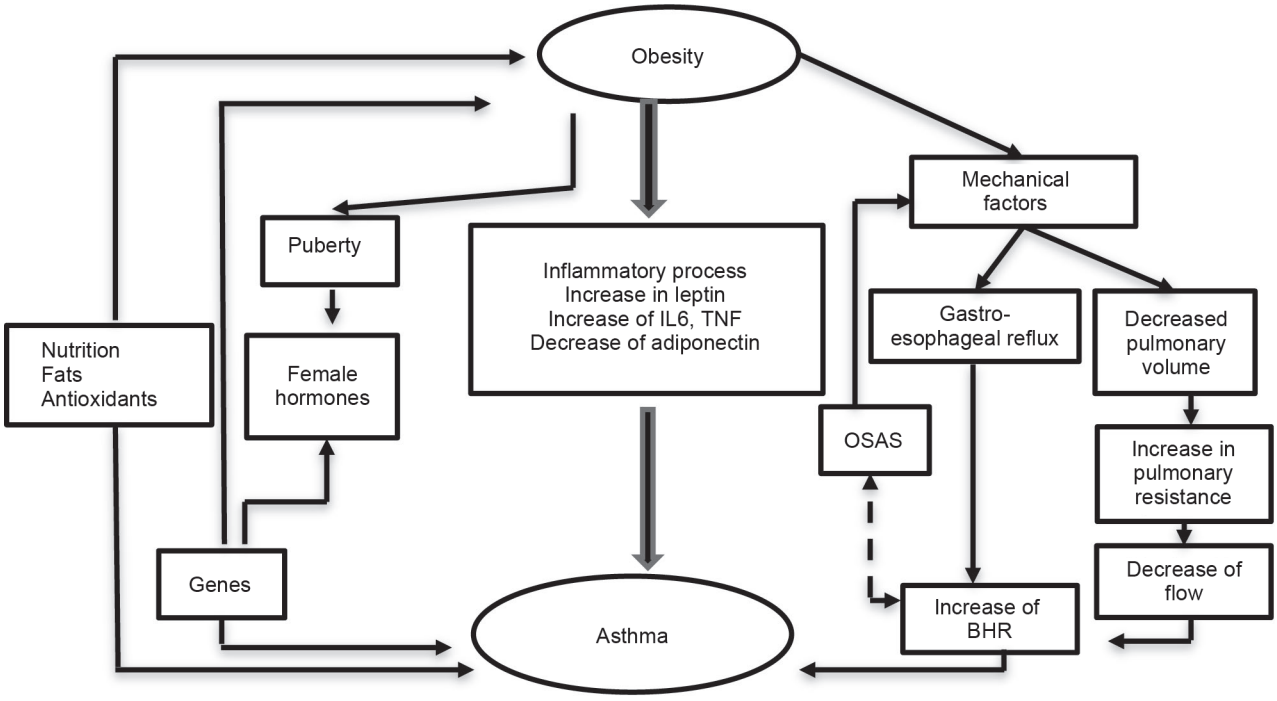

Figure 3. Interrelationships of various factors in obesity and asthma. OSAS, obstructive sleep apnea syndrome; IL6, interleukin 6; TNF, tumor necrosis factor; BHR, bronchial hyperreactivity.

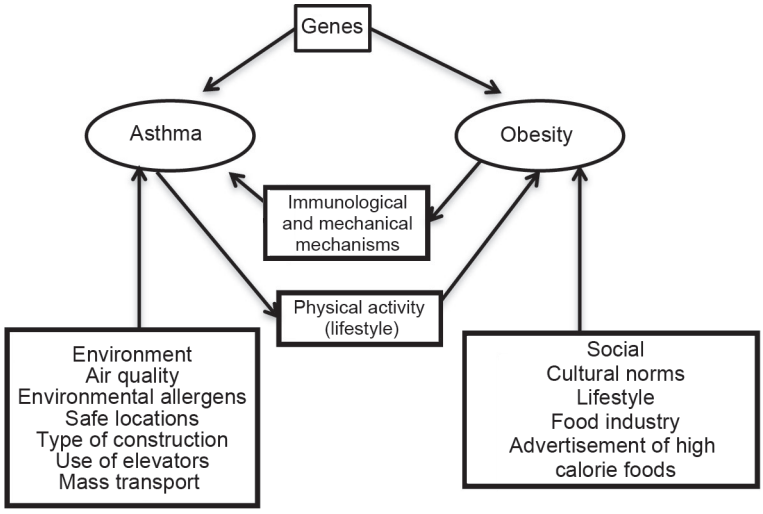

Figure 4. Influence of environmental and social factors in regard to obesity and asthma.

A systematic increase of eotaxin has been found in obese individuals. Part of this chemokine is synthesized in adipocytes and suggests a potential role in asthma risk in obese patients.[100]

Obesity and Metabolic Disorders

Apart from the changes in lung function in asthmatic obese patients, inherent complications of obesity can be found such as changes in blood sugar, blood pressure, lipids and insulin resistance.[101] Compared with the metabolic disorders that cause obesity, there are few studies simultaneously assessing both asthma and obesity. In a group of obese adolescents with and without asthma and nonobese asthmatics, as well as healthy controls, our group found that obese asthmatic males had a greater frequency for metabolic syndrome.[102]

Most prospective epidemiological studies indicate that obesity may increase the prevalence and incidence of asthma, predominantly in postpubertal females. The likelihood of developing asthma in obese school children may be as high as 50%. There is a clear relationship between increased BMI and asthma, suggesting that the risk increases as weight increases. This is confirmed by the effect of weight loss interventions, which are associated with decreased asthma symptoms.

Complex relationships between these two conditions are an example of the interaction between genetics and environment in its pathogenesis. It is very likely that this involves more than one biological mechanism (Figure 5).

Obesity may directly affect the asthma phenotype by mechanical effects, by closure of the airway, and by modulation of cytokines in adipose tissue through common genes or genetic regions or other effects that include estrogen.

More research is needed to elucidate these two phenomena and their many interrelationships. It is clear that weight reduction improves the respiratory health of an asthmatic patient. Therefore, treatment of obese asthmatic patients should include a weight control program, with the premise that obesity alters the normal response to asthma treatment. It is possible that asthma is overdiagnosed in the obese population and is phenotypically different from that experienced by normal weight individuals. However, we should keep in mind that obesity itself causes physiological impairment of lung function with a predominance of a restrictive pattern such as gastroesophageal reflux and sleep apnea that increases oxygen consumption. Excess fatty infiltration contributes to this comorbidity.

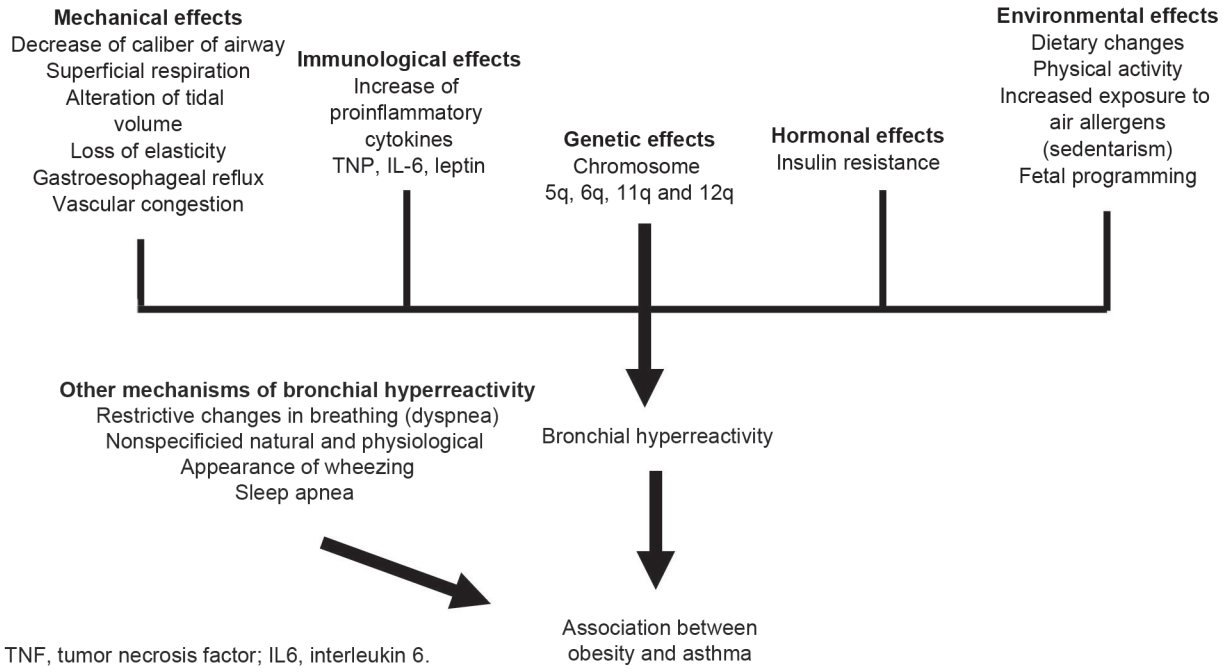

Figure 5. Relationship between hyperreactivity and asthma. Common factors for presentation.

- Obesity is associated with an increased incidence and prevalence of asthma in epidemiological studies.[22-38]
- Fetal programming can affect the subsequent development of chronic diseases such as obesity and asthma.[54,55]
- Obesity may directly affect the asthma phenotype by mechanical effects, causing changes in the airway, gastroesophageal reflux, chronic inflammatory effect of the production of pro-inflammatory cytokines in adipose tissue and through hormonal action predominantly with estrogen.
- We have yet to be able to demonstrate an association between obesity and atopy.[91]
- Obesity may be related to asthma through genetic interactions and environmental exposures (lifestyle, dietary habits).[43]
- Weight loss in obese subjects results in improved lung function and asthma symptoms, as well as reduced use of asthma medications.[57]
- Treatment of obese asthmatic patients should include a weight control program because obesity alters the normal response to drug treatment.[17]

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