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REVIEW

Obesity and asthma: A coincidence or a causal relationship? A systematic review

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Summary

Background and aim: Epidemiological data has established increasing adiposity as a risk factor for incident asthma. However, the mechanisms underlying the association between obesity and asthma are incompletely understood. In the present paper, we review current knowledge of possible mechanisms mediating the observed association between obesity and asthma.
Methods: Systematic literature review.
Results: Obesity and asthma share some etiological factors, such as a common genetic predisposition and effects of in utero conditions, and may also have common predisposing factors such as physical activity and diet. Obesity results in important changes in the mechanical properties of the respiratory system which could explain the occurrence of asthma. However, there are also plausible biological mechanisms whereby obesity could be expected to either cause or worsen asthma. These include co-morbidities such as gastro-oesophageal reflux, complications from sleep-disordered breathing, breathing at low lung volumes, chronic systemic inflammation, and endocrine factors, including adipokines and reproductive hormones. Obesity related asthma is in general not associated with eosinophilic airway inflammation, and adipokines are likely to play important roles in the inflammatory pathogenesis of asthma in obese individuals.
Conclusion: The association between obesity and asthma is not straightforward, and further knowledge is clearly needed, as understanding the underlying mechanisms may lead to new therapeutic options for this high-risk part of the asthma population.
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Contents

Introduction

In recent decades, the prevalence of obesity (body mass index (BMI) $\geq$ 30 kg/m^2) has increased dramatically in the US, and the prevalence is also increasing rapidly in most European countries, and is estimated to increase further.[1,2] Obesity is associated with a high risk of chronic diseases, including diabetes and cardiovascular disease, and thus constitutes a major public health problem.[3]

Asthma is also a major health problem estimated to affect more than 300 million people of all ages and ethnic backgrounds worldwide.[4] Since Camargo et al.[5] first described the association between obesity and asthma, numerous epidemiologic studies published during the past decade have demonstrated an increased risk of asthma and asthma-like symptoms in obese individuals[5–8] and, furthermore, there seems to be a dose response effect of increasing BMI on asthma incidence.[6] Obesity is associated with increased asthma severity in both children and adults.[9–13] Taylor et al.[14] reported that obesity is associated with increased daily asthma symptoms, missed workdays, increased use of rescue bronchodilator and an overall increase in asthma severity. Obesity is also associated with less likelihood of achieving well-controlled asthma and less-favourable response to current asthma therapy.[15–21]

Preliminary data suggest that obese patients with asthma demonstrate different asthma phenotypes compared with patients of normal weight.[22–24] The obese asthma phenotype can be reversed by weight loss with improvements in lung function, severity of asthma symptoms, and by that overall asthma control as well as decreased medication utilization and hospitalizations.[25–29]

The aim of the present review is to give an overview of the possible mechanisms underlying the observed association between obesity and asthma.

Methods

A series of searches were carried out, last updated February 2013, using the database PubMed. The strategy was intended to be broad in order to maximize the capture of citations for peer-reviewed publications relevant to asthma and obesity. The PubMed searches were carried out using the following algorithm of MeSH terms: Asthma, asthma-like symptoms AND obesity or overweight, and the searches were repeated with these terms in combination with pathogenesis, mechanisms, genetic, epigenetic, gender, inflammation, oxidative stress, hormones, adipokines, gender and comorbidities. The citation pool was further supplemented from manual assessment of the reference lists accompanying other systematic reviews of aspects related to asthma in obese individuals and from other publications identified as being relevant for further review.

Results

The effect of obesity on lung mechanics

The mechanical effects of obesity on respiratory seem to be relatively straightforward. The most consistently reported effect of obesity on lung function is a reduction in the functional residual capacity (FRC), and studies have revealed an inverse relationship between BMI and FRC.[30,31] The FRC is reduced in obese subjects primarily because of the changes in the elastic properties of the chest wall.[32] The retractive forces of the lung parenchyma on the airways are reduced at low lung volumes, and a lower FRC may unload the airway smooth muscle (ASM), so that it shortens more when activated either by a physiological increase in parasympathetic tone or in response to bronchoconstrictor agents.[33] Low tidal volume (V_T) may also contribute to a further reduction in the strain on ASM. Obese humans

breathe spontaneously with lower V_T and higher frequencies than their lean counterparts.[34] Attachment of each myosin head to actin imparts increased stiffness to the muscle, hence not only does breathing relaxes ASM, it also makes it more compliant and easier to stretch with each breath. The amplitude of fluctuations in force that strain ASM is closely linked to the peribronchial stress. Stretching of ASM during breathing causes actin-myosin cross-bridges to detach: the bigger the tidal volume (stretch), the greater the ensuing bronkodilatation.[35] The cross-bridge attachment can also increase the stiffness of ASM, making the muscle harder to stretch. Because obese subjects breathe with lower V_T, the obesity-related reductions in V_T may lead to a self-sustaining loop, i.e. lower V_T leading to smaller ASM strain leading to greater ASM stiffness, and greater stiffness leads to even less ASM strain with each tidal breath. The net result is likely to be more substantial ASM contraction, increased muscle shortening and airway narrowing. Closing volume, defined as the volume of gas remaining in the lungs when the small airways begin to close during a controlled maximum exhalation, normally increases with age and is also known to be increased in individuals with airflow limitation. The effects mentioned above may therefore be enhanced by tidal breathing around the closing volume.[36–39] In morbid obesity, tidal breathing usually takes place around the closing volume,[40,41] and small airway closure is observed in many obese subjects during tidal breathing, particularly in the supine position.[40,42,43] It has been suggested that the repeated opening and closing of peripheral airways that occurs under such circumstances may lead to rupture of alveolar attachments to bronchioles,[44] uncoupling the airways from the retractive forces of the lung parenchyma, and by that lead to worsening of airflow limitation (Fig. 1).

Spirometric variables, such as forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), also tend to decrease with increasing BMI.[45] It has been suggested that the association between increasing BMI and a decrease in lung function is due to the fact that adiposity mainly compresses the chest, also from the sub-diaphragmatic angle, and by that limits the expansion of the lungs.[45,46] However, the exact dose–response relationship between the amount and distribution of body fat and the mechanical changes remains unknown and further knowledge is clearly needed.

Obesity, inflammation and asthma

Obesity in humans is, even in the absence of any overt inflammatory insult, associated with persistent low-grade systemic inflammation, and there is increasing evidence that obesity should be regarded as a pro-inflammatory state.[47] Adiposity contributes to the pro-inflammatory milieu and is thereby responsible for the formation of low-grade chronic inflammation in obese individuals.[48] Visceral adipose tissue is an important source of cytokine production. It has been shown that high-sensitivity C-reactive protein (hsCRP), tumour necrosis factor-alpha (TNF-α) and interleukin (IL)-6 concentrations is higher in obese than in non-obese individuals. In obese individuals, obesity, assessed by BMI, is significantly correlated with hsCRP concentration, whereas visceral adiposity is
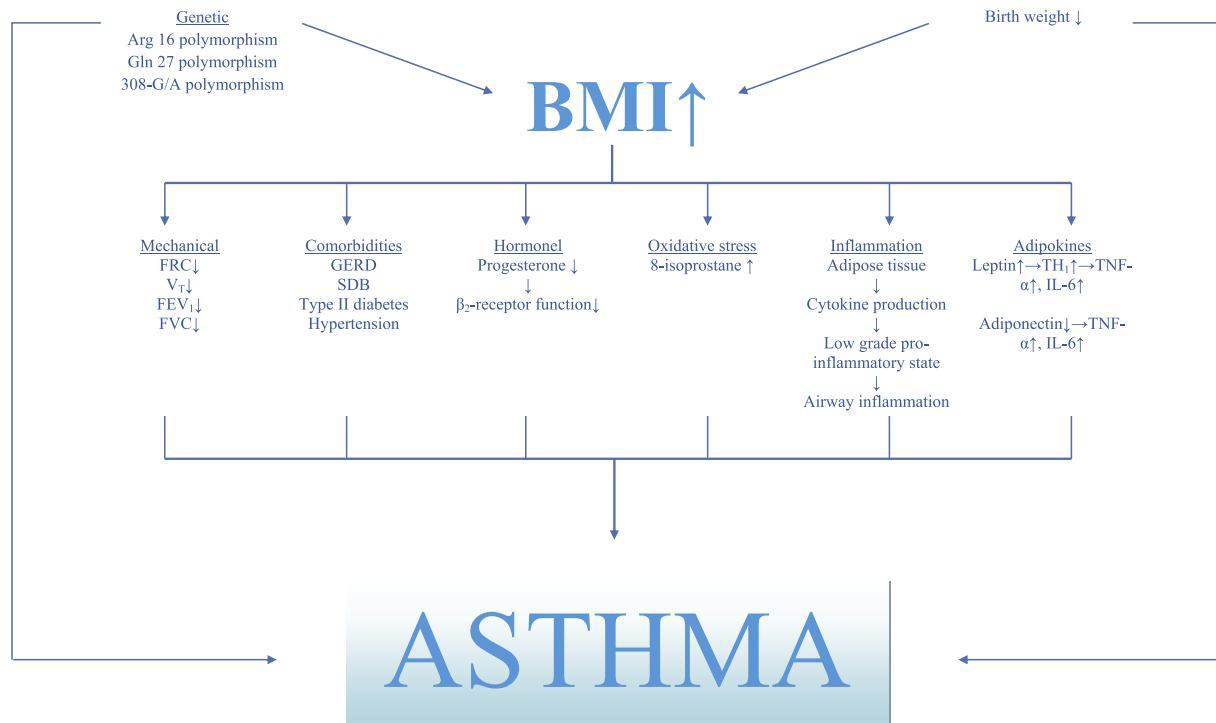

Figure 1 Schematic presentation of the possible mechanisms that may explain the observed association between obesity and asthma.

significantly associated with IL-6 concentration.[48,49] However, the effect of systemic inflammation on airway inflammation in asthma is debated and only incompletely understood. The low-grade chronic pro-inflammatory state seen in obese subjects affects the cellular and molecular signalling pathways of the immune system, and it has been proposed that systemic inflammation modulates airway inflammation and, consequently, the expression of asthma in obese subjects.[50] However, the effects of obesity on systemic inflammation are unlikely to fully explain the asthma—obesity association observed in humans.[51,52]

A positive correlation between adipocyte diameter and TNF-α level has been observed and this finding is in agreement with the known biological relationships between body fat and metabolic diseases in adults. It emphasize that subcutaneous adipocyte diameter is an adiposity measure more closely related to inflammation than BMI or fat mass. Both BMI and fat mass are surrogate indexes of adipocyte size.[53] Asthma is characterized by the presence of an inflammatory cell infiltrate in the bronchial mucosa consisting of activated mast cells, eosinophils, and T-lymphocytes. Several cytokines are considered to play a pivotal role in this response, particularly IL-4, IL-5, IL-6, and TNF-alpha. TNF-α is known to be elevated in uncontrolled, severe asthma. TNF-α also increases the production of Th2 cytokines such as IL-4 and IL-5 in bronchial epithelium and in addition, it is involved in the recruitment of neutrophils, eosinophils, and T cells into the inflammatory zone. IL-4 stimulates activated B-cell and T-cell proliferation, and the differentiation of CD4+ T-cells into Th2 cells. IL-4 also plays a pivotal role in the regulation of IgE synthesis and induces the expression of the low-affinity IgE receptor on macrophages. IL-5 is a growth and differentiation factor, activator, and chemo-attractant for eosinophils and as a consequence is considered a pivotal cytokine in allergen- and parasite-mediated eosinophilic responses. IL-5 stimulates B cell growth and increase immunoglobulin secretion Furthermore, TNF-α also increases the production of pro-inflammatory cytokines such as IL-6 and IL-1β.[54] Thus, the TNF-α inflammatory pathway is common to both obesity and asthma and it is plausible that this pathway is up-regulated in the presence of both asthma and obesity, and by that leading to higher levels of these cytokines due to the higher levels of TNF-α. TNF receptors are expressed in ASM cells and TNF-α may increase contractility in response to airway constrictor agents; or in other words they might increase airway hyperresponsiveness.[55] Airway hyperresponsiveness is a characteristic feature of asthma and a causal link between airway inflammation and airway hyperresponsiveness in asthma is favoured by many.[56] However, most studies have not been able to demonstrate an association between obesity and increased airway inflammation in asthma.[57–60] A prospective study by Sutherland et al.,[61] demonstrated increased IL-1β, IL-5, IL-6 and IL-8 in sputum supernatants obtained from individuals with asthma, but no differences were noted between obese and lean patients leading the authors to conclude that the obese asthma phenotype is not a result of more pronounced airway inflammation. TNF is known to act via TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). Zhu et al.[62] have, in obese mice, studied the role of TNFR1 for characteristics of airway hyperresponsiveness. The authors observed that obesity resulted in systemic as well as pulmonary inflammation, but that activating TNFR1 seems to protect against the airway hyperresponsiveness associated with obesity, and, therefore, may suggest that effects on pulmonary inflammation contribute to this protection. In another experimental mice study, Williams et al.[63] have shown that TNFR2 signalling is required for the innate AHR that develops in obese mice, and based on their observations, suggested that TNFR2 may act by promoting endothelin.

Eosinophil airway inflammation can be quantified by the percentage of eosinophils in induced sputum or indirectly by the level of nitric oxide in exhaled breath. However, previous studies have failed to document an association between body fat and exhaled nitric oxide, as a marker of eosinophilic airway inflammation.[64] Farah et al.[65] reported residual asthma symptoms in obese patients after anti-inflammatory treatment leading to significant reductions in exhaled nitric oxide. Veen et al. studied a group of severe asthmatics in a tertiary care setting, and found that BMI was inversely related to both sputum eosinophilia and exhaled nitric oxide.[58] The current evidence, therefore, suggests that obesity does not increase the degree of eosinophil airway inflammation in asthmatics, and that obesity related asthma is mediated primarily through non-eosinophilic pathways.

Oxidative stress, obesity and asthma

In case of oxidative stress, either an increased reactive oxygen species (ROS) production and/or reduced antioxidant defences create an imbalance, allowing for oxidative insult to occur, which can worsen inflammation and lead to injury by enhancing pro-inflammatory cytokine release and altering enzymatic function.[66] Compared with non-asthmatic subjects, subjects with asthma have increased systemic oxidative stress.[67] An increased oxidative stress in asthma may be associated with an increased production of lipid peroxidation products and protein carbonyls in plasma, increased plasma isoprostanes, enhanced generation of ROS by blood monocytes, neutrophils, and eosinophils; increased oxidized glutathione in bronchoalveolar lavage (BAL) fluid, and increased level of nitric oxide (NO) in exhaled air. In children, asthma is associated with increased exhaled breath condensate levels of malondialdehyde (MDA) and reduced glutathione.[68,69] Glutathione, in its reduced form, protects airway epithelial cells from free radicals, while MDA is formed due to the action of reactive oxygen species on membrane phospholipids and is a marker of oxidative stress. Ercan et al.[70] showed that plasma MDA levels are increased and glutathione levels are decreased in children with asthma, with the highest levels of oxidative stress seen in children with more severe disease. Furthermore, children with asthma had higher plasma levels of 8-isoprostanes, a prostaglandin and a biomarker of oxidative stress, compared with healthy controls. Montuschi et al.[71] showed that airway oxidative stress could be assessed by sampling 8-isoprostanes in exhaled breath condensate (EBC). In their study, the EBC concentration of 8-isoprostanes in asthmatic subjects correlated with the fraction of exhaled nitric oxide. The concentration of 8-isoprostanes increased with increasing severity of asthma;

and the average concentration was higher in asthmatic subjects than in healthy controls. The available data support the assumption that asthma is associated with increased oxidative stress.[72] However, it is unclear if the presence of increased airway oxidative stress is a consequence of the more pronounced systemic oxidative stress seen in obesity.

Obesity is also associated with increased oxidative stress and systemic inflammation,[73] and in cross-sectional studies, obese subjects have higher levels of oxidative stress biomarkers compared with their normal-weight counterparts.[74] Increased systemic or airway oxidative stress may, therefore, potentially be the mechanism linking obesity with increased asthma severity. Whether or not exhaled 8-isoprostane levels in asthmatic subjects are correlated with BMI was evaluated in the study by Komakula et al.[75] Sixty-seven patients aged 18—70 years previously diagnosed with moderate to severe persistent asthma according to the GINA guidelines[4] were enrolled and compared with 47 healthy controls recruited from the hospital personnel. There was a linear association between BMI and exhaled 8-isoprostanes in the 67 moderate to severe adult asthmatic subjects, but not in the 47 healthy controls. However, no test for interaction was reported, and the average levels of exhaled 8-isoprostanes were not different between asthmatic subjects and controls. In a cross-sectional study, Sood et al.[76] investigated the association between plasma levels of 8-isoprostanes and BMI and found that BMI was positively associated with 8-isoprostanes, but only in women. In the un-adjusted analysis, asthma was significantly associated with increased 8-isoprostanes, but this association became non-significant after adjusting for BMI. Among women, there was a significant association between increasing BMI and the presence of asthma, whereas there was no significant association with 8-isoprostanes. These results suggest that obesity is associated with asthma, yet this association is not explained by increased systemic 8-isoprostanes. Holguin et al.[77] measured serum and exhaled 8-isoprostane levels in a cohort of moderate to severe adult asthmatics. The presence of obesity, but not asthma, was associated with increased exhaled 8-isoprostane levels. On the other hand, plasma levels of 8-isoprostanes were higher in asthmatics, but no effect of obesity was observed. In addition, there was no correlation between exhaled and plasma 8-isoprostane levels. Based on these data, the authors inferred that while asthma increases systemic oxidative stress and obesity increases airway oxidative stress there was no synergism between plasma and exhaled 8-isoprostane levels. It is difficult to make a conclusion regarding the role of oxidative stress in obese asthmatics given the conflicting currently available data, but it is plausible that oxidative stress may not be a causative factor but rather may modulate asthma severity and alter response to medications.

Adipokines in obesity related to asthma

Adipose tissue produces a number of mediators, termed adipokines, which have significant metabolic effects. One of these adipokines, named leptin, is secreted by adipose tissue in direct proportion to the level of adiposity,[78] and acts, under healthy conditions, through the hypothalamus as an appetite suppressant and metabolic stimulant.[79]

Leptin stimulates the production of inflammatory mediators such as TNF-α and IL-6 from the adipose tissue,[80,81] TNF-α also promotes the expression and release of leptin from the adipose tissue,[82,83] and thereby establish a positive feedback mechanism. Leptin promotes CD_4 (+) T lymphocyte activation towards the Th1 phenotype with increased production of interferon-γ.[84—86] Leptin thereby leads to production of pro-inflammatory cytokines, including TNF-a, IL-6 and interferon-γ, well-known to be associated with asthma.[87,88] However, the effects on Th1 and Th2 cytokines differ. Leptin increases Th1 cytokine production (IL-2, interferon-γ and TNF-α), but decreases Th2 cytokine production (IL-4, IL-5, and IL-10). These observations suggest that, if leptin plays a role in asthma, it is unlikely to be through a traditionally Th2 phenotypes of asthma. The pro-inflammatory effect of leptin is also mediated by monocytes, and macrophages respond to leptin through increased lipopolysaccharide (LPS)-stimulated production of cytokines.[81,84,89] Furthermore, leptin is also capable of promoting angiogenesis and airway remodelling via vascular endothelial growth factor (VEGF), as VEGF release from human ASM cells is enhanced following leptin stimulation.[90] Therefore, leptin is assumed to have a more vital effect on the asthmatic inflammation, and perhaps also airway remodelling, in obese than in non-obese individuals suffering from asthma. Sood et al.[91] have in a large cross-sectional, population-based US study showed a positive association between the highest quartile of serum leptin concentration and the presence of current doctor-diagnosed asthma in women. After adjustment for serum levels of leptin, the relationship between BMI and asthma was attenuated but remained of borderline significance. These findings, therefore, suggest that the leptin pathway may partly explain the obesity—asthma relationship.

Adiponectin levels, in contrast to many of the other adipokines, decreases in obesity and increases again with weight loss, and plasma adiponectin levels are, therefore, inversely related to BMI.[92—96] Adiponectin have primary metabolic effects in the liver and skeletal muscle, including increased glucose uptake, inhibition of gluconeogenesis, and increased fatty acid oxidation, and, furthermore, adiponectin also has anti-inflammatory effects.[96—101] These anti-inflammatory effects of adiponectin are inhibition of the production of the pro-inflammatory cytokines IL-6 and TNF-α[102] and induction of the anti-inflammatory cytokine IL-1 receptor antagonist and IL-10.[103,104] Adiponectin markedly attenuates allergen induced airway inflammation in mice[105] and adiponectin deficient mice demonstrate greater eosinophilia in the airways.[106] In premenopausal women, serum adiponectin — proteins mainly produced by adipocytes which may be pro-inflammatory (such as leptin) — levels are protective against the development of asthma.[107] Low adiponectin levels have also been associated with asthma in population studies.[108]

Epigenetic mechanisms associated with obesity and asthma

There is growing recognition that prenatal and early-life diet and nutrition may be important for the development of both asthma and obesity, as well as other diseases. Current

evidence suggests that specific elements of prenatal diet, e.g. apples, fish, and egg, and specific nutrients in prenatal diet, including antioxidants, vitamin E and C, zinc, selenium, iron, fatty acids, and vitamin D, may influence asthma and allergies through effects on the neonates immune system and lung development.[109–117] Intrauterine nutrition may influence the risk of subsequent obesity through perturbations of the central endocrine regulatory systems and programming the development of adipose tissue in the offspring.[118,119] The associations between birth weight and subsequent obesity and asthma strongly suggest that prenatal nutrition plays a role in the development of both of these conditions, although the mechanisms may differ. However, we do have some evidence suggesting that the development of obesity and asthma is influenced by common events. Low birth weight is associated with increased body fat, primarily abdominal fat, later in life.[120] With respect to asthma, Raby et al.[121] reported a strong relationship between low-normal gestational age (born in the 36th week of gestation or later) and asthma at 6 years of age. However, they did not observe similar association between low birth weight and asthma at 6 years of age. Others have also reported that intrauterine growth retardation is a risk factor for adult asthma.[122,123] Low birth weight is associated with lower level of lung function in adulthood,[124] and small lung size is a known risk factor for doctor-diagnosed asthma and episodes of wheezing,[125] probably because small lung size results in reduced airway calibre. Several studies have shown that there is a U-shaped relationship between birth weight and adult BMI, so that both low and high birth weights are associated with obesity in adulthood.[126–128] Both low and high birth weights are also associated with later asthma.[8,129,130]

Because both asthma and obesity appear to have their roots in utero and in early childhood, common exposures that predispose individuals to both these conditions may explain the association. Future research is, therefore, clearly needed and may, hopefully, provide insight into these early-life factors and by that facilitate prevention of these disorders.

Genetic influences on asthma and obesity

Asthma and obesity may partly share genetic origin. Hallstrand et al.[131] analysed 1001 monozygotic and 383 dizygotic same-sex twin pairs by using structural equations models to estimate the magnitude of shared genetic cause that could explain the association between asthma and obesity. The authors reported that a substantial proportion of the phenotypic variation in asthma and obesity was a result of genetic effects and that a large part of the covariation between obesity and asthma was controlled by genetic factors. This study, in line with other studies, provides evidence for genetic pleiotrophy, i.e. that a common set of genes increases the susceptibility to both asthma and obesity. Moreover, their analysis showed that approximately 8% of the genetic component of obesity is shared with asthma. In fact, specific regions of the human genome have been identified as related to both asthma and obesity. Chromosome 5q contains genes ADRB2 and NR3C1. ADRB2, the gene that codes for the adrenergic β2 receptor,

influences sympathetic nervous system activity and is important in regulating not only the airway tone but also the resting metabolic rate. The gene encoding for the β2 adrenergic receptor is located on chromosome 5q31–q32. The Agr16 polymorphism of this receptor has not been associated with asthma per se,[132] but has been associated with certain asthma phenotypes, including nocturnal asthma,[133] and treatment response to especially long-acting β2-agonists,[134] although the clinical importance of the latter has been disputed. The Gln27 polymorphism of the β2-adrenergic receptor has been found to be significantly associated with obesity.[135,136] Polymorphism of the Gln27 influences the bronchodilator response to β2-agonists.[137] NR3C1, which codes for the glucocorticoid receptor, is also located on chromosome 5q31–32, and is related to both asthma and obesity.[138–141] Polymorphism of the NR3C1 gene is significantly associated with bronchial asthma and may play an important role in the development of difficult-to-control asthma,[142,143] but the mechanisms behind this are only incompletely understood. Body fat distribution is influenced by non-pathologic variations in the responsiveness to cortisol, and genetic variations in the glucocorticoid receptor influence the accumulation of abdominal visceral fat,[140] as well as the overall presence of obesity and overweight.[144,145] Individuals with specific variations in the glucocorticoid receptor are, therefore, more likely to have both increased BMI and a higher risk for developing asthma. Furthermore, their increased BMI is also associated with a higher risk for asthma. Future studies will hopefully provide further insight into the genetic influence of the obesity–asthma association.

The TNF-α gene complex is located on chromosome 6p21.3 and influences the immune and inflammatory response important in both asthma and obesity. Several studies have found associations between the 308-G/A polymorphism of the TNF-α gene and both asthma[146] and obesity.[147] The NcoI variant in the lymphotoxin-A gene (LTA, 6p21.3), interacting with the 308-G/A polymorphism of TNF, has been associated with various asthma-related phenotypes including atopic asthma,[148,149] whereas the T60N polymorphism of the LTA gene has been associated with waist circumference and other phenotypes of the metabolic syndrome.[150]

Chromosome 12q contains genes for inflammatory cytokines associated with both asthma[151] and obesity.[151,152] Several variants in the vitamin D receptor gene (VDR, 12q13) have been associated with asthma-related phenotypes.[153–155] Vitamin D metabolites are important immune-modulatory hormones and are able to suppress Th2-mediated allergic airway disease.[156] In Chinese adults with asthma, vitamin D deficiency has been associated with decreased lung function.[157] In Italian children, lower levels of serum vitamin D are associated with reduced lung function, increased hyperresponsiveness to exercise, and poorer asthma control.[158,159] Finally, some authors[160,161] have suggested that chromosome 11q13 is also related to asthma and obesity, but this is at present controversial. Chromosome 11q13 contains UCP2, UCP3 and the low-affinity immunoglobulin E receptor FCεRB. The UCP2 and UPC3 are uncoupling proteins having an influence on the metabolic rate,[162] but their contribution to variation of obesity phenotypes in the general population remains

controversial. Some researchers have even suggested that the UCP2/UCP3 genes are unlikely to have a substantial effect on variation in obesity phenotypes in US Caucasians.[163] In contrast, the low-affinity immunoglobulin E receptor has been linked with asthma and some believes that the low-affinity immunoglobulin E receptor forms part of the inflammatory response of Th2 cells, whose levels increase in asthma, but not in obesity,[164] but also this is controversial, as some studies have failed to show the evidence for a role of chromosome 11q13 in atopy and asthma.[165,166] However, recent analyses based on the genome-wide association (GWAS) studies have concluded that single nucleotide polymorphisms (SNPs) within several genes showed associations to both BMI and asthma at the genetic level, but none of these associations were significant after correction for multiple testing.[167]

Gender differences in the asthma—obesity association

Several cross-sectional studies have found a relationship between obesity and asthma only in females,[168–171] and many prospective studies have also found either no effect in men or a greater effect in females than in men.[172–175] In a survey of 19.126 Dutch adults, women with a BMI of >30 had 1.8 times higher risk of self-reported asthma than non-obese women.[176] The observed gender difference may be related to the sex hormone oestrogen. Adipose tissue is recognized as metabolically active, and in obesity androgen levels are increased. However, peripheral aromatisation of androstendione to oestrone and testosterone to oestradiol occurs within the stroma of adipose tissue.[177] During the menstrual cycle, peak oestrogen levels have been associated with increased symptoms and decreased pulmonary function in asthmatic women,[178] and independent data from the Nurses' Health Study I suggest that exogenous oestrogen is an independent risk factor for the development of incident asthma in adult women.[179] In line with this, Lange et al. have reported that postmenopausal women on hormonal replacement therapy have a slightly higher risk of asthma and asthma-like symptoms.[180] A study on mice has shown that administration of β-oestradiol in female mice results in a shift in the immunological reaction from a Th1 to a Th2 type.[181] Studies have demonstrated that γ-oestradiol increases IL-4 and IL-13 production from blood monocytes,[182] and increases both eosinophil recruitment[183] and degranulation.[184] These effects of oestradiol, therefore, exemplify those typically found in asthma.

Obesity decreases progesterone levels,[185] whereas progesterone up-regulates the number of $β_2$-receptors. A reduction in progesterone levels reduces $β_2$-receptor function, which in turn reduces bronchial smooth muscle relaxation.[186] As described above, the satiety hormone leptin is produced by adipose tissue and may promote asthma via effects on immune and inflammatory cells. Leptin concentrations are 4–6 times greater in severely obese compared to lean human subjects.[187,188] Importantly, for equivalent BMI, leptin levels are higher in women than in men.[188–190]

The relationship between obesity and asthma appears more clearly in women than men. Taken together, these results suggest a modulating effect of sex hormones on the expression of asthma in obesity, but the pathways involved needs to be further investigated.

Comorbidities of obesity and asthma

Obesity may increase the risk of asthma through its effects on other disease processes. Comorbidities of obesity, such as gastroesophageal reflux disease (GERD), sleep-disordered breathing (SDB), dyslipidaemia, type II diabetes, and hypertension may trigger or aggravate asthma.

Obesity increases the risk of both GERD and SDB.[191–195] Patients with GERD have a significantly higher risk of concurrent asthma compared with patients without GERD,[196–198] and the same is observed for patients with SDB.[16] GERD can worsen asthma either by direct effects on airway responsiveness or via aspiration-induced inflammation. Obesity is associated with relaxation of the gastro-oesophageal sphincter, resulting in reflux of stomach acid up the oesophagus and into the airways. Direct contact of stomach acid with the airways leads to bronchoconstriction either by microaspiration or by vagally mediated reflux.[199] Two large epidemiologic studies have systemically examined the interrelationships between these conditions. Multivariate logistic regression analysis of data from over 16.000 participants aged 20–44 in the European Community Respiratory Health Survey demonstrated that the relationship between obesity (BMI>30) and onset of asthma was unaffected by adjustment for GERD or habitual snoring.[191] Although long-standing GERD is thought to contribute to on-going airway inflammation in asthma, direct evidence of such a relationship is, at best, limited.[200] Similarly, Sulit et al.[201] demonstrated in a community-based cohort study of 788 children aged 8–11 years) that adjustment for SDB attenuated the association between obesity and wheeze, but did not substantially alter the association between obesity and asthma. Taken together, these data suggest that the increased risk of asthma in obese individuals is independent of GERD and SDB.

Dyslipidaemia is a common comorbidity of obesity. A recent study from Al-Shawwa et al.[202] indicates a higher prevalence of asthma in children with high serum cholesterol, suggesting that hypercholesterolemia is a potential risk factor for asthma independent of obesity, but these data has not yet been reproduced, and similar studies in adults are also needed.

Type II diabetes is also a common complication of obesity. There are data indicating that asthma is less prevalent in patients with type I diabetes.[203] Animals with experimentally induced type I diabetes also have reduced airway responsiveness and reduced airway inflammation following allergen sensitization and challenge, and these effects are reversed after exogenous administration of insulin.[204–206] It has therefore long been speculated whether there is a relationship between type II diabetes and asthma, because type II diabetes is often characterized by hyperinsulinaemia. A recent report[207] indicates a higher prevalence of insulin resistance among obese children with asthma versus obese children without asthma, leading to the assumption that the pro-inflammatory state of insulin resistance may contribute to the pathogenesis of asthma in

obese patients. However, these findings should be reproduced in other studies before valid conclusions may be drawn.

Hypertension is very common in the obese individual.[208,209] Hypertension leading to diastolic heart failure and ensuing pulmonary congestion could amplify peribronchial oedema as a result of volume expansion. Oedema of the airways has been proposed to augment airway narrowing by uncoupling the airways from the retractive forces of the lung parenchyma.[210] Increased systemic levels of endothelin are also common in obesity-related hypertension[211] and endothelin is a potent bronchoconstrictor.[212]

The association between obesity and asthma symptoms might be an epiphenomenon, and therefore that the true association is due to comorbid conditions or lifestyle factors associated with obesity, however, available evidence of causation or a significant association is, at best, limited.

Impact of environment and behaviour on obesity and asthma

It is conceivable, that the association between obesity and asthma might be mediated just through low levels of physical activity. In the EPIC Norfolk cohort, various indicators of physical activity showed that persons engaged in more active leisure activities had better respiratory function than persons with a more sedentary lifestyle, and that those who were engaged in more vigorous leisure—time activities had a slower decline in FEV_1.[213] In a longitudinal study, daily physical activity was positively related to FVC but not to FEV_1.[214] Rasmussen et al.[215] have shown that increased physical fitness is associated with decreases in the relative risk of incident asthma in schoolchildren.

Active cigarette smoking has been associated with the development of asthma in some studies.[216–218] However, the association between BMI and asthma remains even after adjusting for smoking. Unemployment is directly associated with higher BMI[219,220] and there is also an independent associations between BMI, limited physical activity and spending many hours on TV-watching.[220] It is conceivable, that obese people are more likely to stay at home and thereby are more exposed to the indoor surroundings, and it is well known that exposure to e.g. allergens and chemicals in the indoor environment can lead to the development of asthma.[221,222]

Patients with asthma may be at increased risk of becoming obese if they avoid exercise, which might trigger their symptoms, and/or as an adverse effect of corticosteroid therapy. However, prospective longitudinal studies have shown that obesity antedates asthma.[223–225] The largest prospective study[226] followed over 135.000 Norwegian men and women for an average of 21 years. Asthma was self-reported, and height and weight were measured at baseline. In men, beginning at a BMI of 20, the incidence of asthma increased steadily at a rate of 10% per unit increase in BMI. In women, there was a 7% increase in the incidence of asthma per unit increase in BMI, beginning at a BMI of 22. While in this study, the relationship between obesity and asthma was at least as strong in men as in women, gender differences in the relationship between obesity and asthma have been reported by others (see gender differences above).

Discussion

There is substantial evidence that obesity and asthma are related. Obesity-associated asthma may be a unique phenotype of asthma, characterized by decreased lung volumes, more pronounced symptoms, less likelihood of achieving good asthma control, non-eosinophilic airway inflammation and a less-favourable response to controller medication. Whether this relationship between obesity and asthma is causal or represents co-morbidity due to other factors is not yet clear. Since obesity is a component of the metabolic syndrome, which is also associated with systemic inflammation, it is to be expected that there is a relationship between the metabolic syndrome and asthma.[227] In some studies, insulin resistance or metabolic syndrome is a stronger risk factor than body mass. There is growing evidence of the influence of hyperglycemia, hyperinsulinemia, and insulin-like growth factors on airway structure and function.[228] In a large population-based study in Korea, with over 10,000 participants, the presence of the metabolic syndrome was associated with asthma-like symptoms.[229]

Up until now, several studies exploring the link between obesity and the prevalence and incidence of asthma in adults have been published, the majority of these studies concluded that antecedent obesity was associated with a significant increased annual risk of a new diagnosis of asthma. In addition, there was a dose—response effect to this relationship, with increasing BMI being associated with increasing odds of incident asthma.[6] The question has been raised whether the link between asthma and obesity is real or may be due to misdiagnosis of asthma in obese persons complaining of breathlessness. Pakhale et al.[230] have studied the possible misdiagnosis of asthma in obese people and concluded that obese subjects with urgent health-care visits for respiratory symptoms were most likely to receive a misdiagnosis of asthma. Misdiagnosis of asthma was reported to occur in up to 30% of patients. Health-care providers, and not least doctors, should adhere to guidelines and seek to objectively confirm a diagnosis of asthma in order to avoid falsely labelling some obese patients as having asthma. Moreover, most of the published studies have relied on self-reporting of physician diagnosis of asthma and/or recall questionnaires for respiratory symptoms and medications. This is a major caveat for most asthma and obesity studies thus far. Aaron et al.[231] demonstrated in a randomly selected Canadian adult population that about 30% of self-reported physician-diagnosed subjects with asthma, obese and normal weight alike, did not have objective physiologic evidence of asthma and presumably received a misdiagnosis.

It has been indicated that asthma is not homogeneous and that the association between asthma and obesity may be more for certain phenotypes of asthma. Emerging data suggest at least two possible distinct phenotypes of obese asthma patients[1]: early-onset, atopic asthma that is complicated by coexisting obesity (found in both sexes) and[2] late-onset, non-atopic asthma that is caused by obesity (found predominantly in women).[232,233] Especially, obese individuals with non-atopic asthma are increasingly recognized as a distinct phenotype, and their underlying

pathophysiology are likely to be different from the typical lymphocytic and eosinophilic inflammation found in atopic asthma.[233]

Early- and late-onset asthma are recognized as distinct asthma phenotypes with unique clinical and genetic features.[234] Subjects with early-onset asthma (<12 years of age) have a higher likelihood of allergic sensitization and symptoms, a history of eczema, and tend to have higher IgE levels; in contrast, subjects with late-onset asthma have less atopy but greater airway eosinophilic inflammation.[235] On the basis of early and late-onset asthma appearing to be different phenotypes, it is reasonable to hypothesize that they are differentially affected by increases in BMI. Moore et al.[236] have also identified a unique group of mostly older obese women with late-onset non-atopic asthma, moderate reductions in FEV_1, and frequent need for bursts of oral corticosteroid to manage exacerbations as novel asthma phenotypes. Although the longitudinal or cumulative effects of obesity on asthma are not known in subjects with early-onset asthma, obesity has been shown to be an independent risk factor for unremitting asthma beyond puberty.[237] This suggests that there is an early-onset asthma phenotype in which obesity plays a role in the development of persistent asthma. In subjects with late-onset asthma, there are, at least to our knowledge, no studies to date that have evaluated the longitudinal effect of obesity on asthma outcomes or biomarkers of disease activity.

Conclusions

Obesity is associated with a unique asthma phenotype characterized by more severe disease and with variable response to conventional asthma therapies. The mechanistic basis for the association between obesity and asthma is not known, although mechanical, immunological, genetic, epigenetic, hormonal, and environmental pathways have all been proposed. At present it is unclear which of these various pathways that is the dominant mechanism. However, we believe that the systemic inflammation in obesity up-regulates the asthmatic pathway, and this is modified by adipokines and other systemic inflammatory markers. We favour the hypothesis that adipokines play important roles in the inflammatory pathogenesis of asthma in obese individuals. Further understanding of the mechanisms mediating the obese-asthma phenotype would have significant implications for millions of people suffering from asthma and we therefore encourage and look forward to further work on this important topic.

Conflict of interest statement

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