Novel views on endotyping asthma, its remission, and COPD

Carpaij, Orestes

DOI:
10.33612/diss.136744640

Chapter 7

The asthma-obesity relationship: underlying mechanisms and treatment implications

Orestes A. Carpaij, Maarten van den Berge

Curr Opin Pulm Med. 2018 Jan;24(1):42-49

Abstract

Obesity is a worldwide epidemic with a prevalence that has tripled in the last two decades. Worldwide, more than 1.5 billion adults are overweight and more than 500 million obese. Obesity has been suggested to be a risk factor for the development of more difficult-to-control asthma. Although the mechanisms underlying the asthma-obesity relationship are not fully understood, several possible explanations have been put forward. These will be reviewed in this manuscript as well as the implications for the treatment of overweight and obese asthma patients.

Insulin resistance is a possible factor contributing to the asthma-obesity relationship and the effect is independent of other components of the metabolic syndrome such as hypertriglyceridemia, hypertension, hyperglycaemia, and systemic inflammation. Obesity has important effects on airway geometry, by especially reducing expiratory reserve volume causing obese asthmatics to breathe at low lung volumes. Furthermore, obesity affects the type of inflammation in asthma and is associated with reduced inhaled corticosteroids treatment responsiveness.

Obesity induces the development of asthma with a difficult-to-control phenotype. Treatment targeting insulin resistance may be beneficial in obese asthma patients, especially when they have concomitant diabetes. Systemic corticosteroids should be avoided as much as possible as they are not very effective in obese asthma and associated with side-effects like diabetes, weight gain, and osteoporosis.

Introduction

Obesity is a worldwide epidemic with a prevalence that has tripled in the last two decades [1]. Worldwide, more than 1.5 billion adults are overweight (BMI 25 kg/m^2), and more than 500 million obese (BMI 30kg/m^2) [1]. In parallel, the prevalence of asthma has increased during the last 20 years [2]. Obesity has been reported to be a risk factor for the development of asthma and affects its clinical expression toward a more severe and difficult-to-control phenotype [3,4]. In this manuscript, the asthma–obesity relationship and its clinical implications will be reviewed focusing on literature in PubMed of the last 5 years including the most clinically relevant manuscripts in the view of the authors.

Increased risk to develop asthma in overweight and obese study participants

Several studies have shown that overweight (BMI 25 kg/m^2) and obesity (BMI 30 kg/m^2) are associated with a 1.5–2.5-fold increase in the risk to develop asthma [5–7,8,9&]. Rönmark *et al.* [5] investigated 309 cases of new-onset asthma in the Obstructive Lung Disease of Northern Sweden studies and compared them to 309 non-asthmatic controls selected from the Swedish population register. Their data show that overweight (BMI 25 kg/m^2) and obesity (BMI 30 kg/m^2) increase the risk of new-onset asthma by two and 2.7-fold respectively, the risk factor pattern being independent of the presence of allergy. In line with this, Chen *et al.* [6] showed obesity (BMI 30 kg/m^2) to be a risk factor for both allergic and non-allergic asthma. However, some studies were unable to find a link between obesity and the risk of asthma, particularly those investigating children and male individuals [10–13]. A possible explanation may be that the asthma–obesity relationship has a U-shaped pattern with both underweight (BMI<18.5 kg/m^2) and overweight increasing the risk (Figure 1) [14]. Furthermore, an increased BMI does not necessarily reflect a higher fat mass, but could also be because of increased muscle mass, especially in men. Thus, BMI may not be the best way to define obesity. Indeed, some studies found abdominal obesity, defined as a waist circumference more than 88cm in women and more than 102cm in men, respectively, to be a stronger risk factor for asthma than BMI-defined obesity [15–17]. Finally, it should be noted that many epidemiologic studies investigating the obesity-asthma relationship have relied on a doctor's diagnosis of asthma or self-reported asthma. This may have led to an incorrect diagnosis in up to 30% of cases as demonstrated in studies using extensive

lung function testing after withdrawal of inhaled corticosteroids (ICS) [18,19]. However, the percentage of misdiagnosed cases for asthma in these studies was similar in obese and non-obese study participants, making a bias toward an asthma–obesity relation unlikely [18,19].

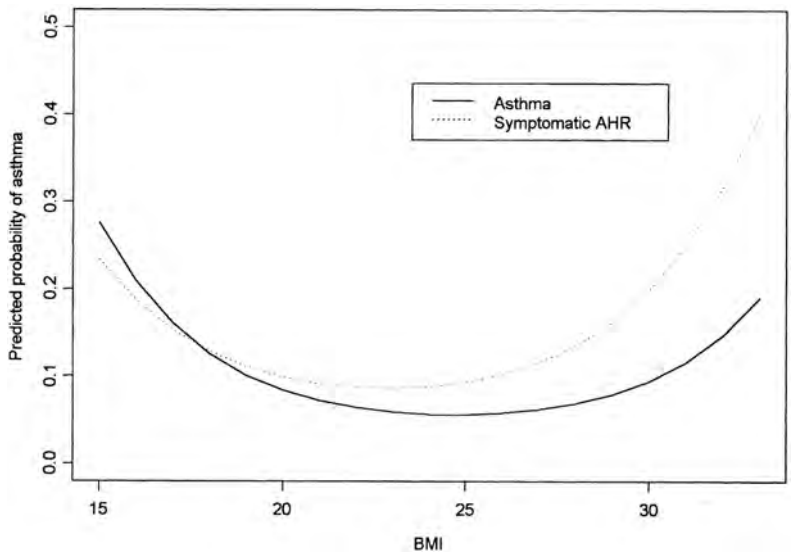

Figure 1: the relation between BMI and risk of asthma in 3386 men in Anqing, adjusted for age, intensity of cigarette smoking, skin, test reactivity to one or more allergens, and familial correlations. Reprinted with permission (Celedón JC et al. Am J Respir Crit Care Med. 2001 Nov 15;164(10 Pt 1):1835-40).

Physical activity, obesity, and the risk to develop asthma

Reduced physical activity has been put forward as a possible mechanism to explain the relationship between obesity and asthma [20]. A systematic review and meta-analysis concerning the association between physical activity and asthma identified 39 cross-sectional studies (n = 661 222) and five longitudinal studies (n = 85,117) [21]. Indeed, the cross-sectional studies observed an association between high physical activity and low asthma prevalence suggesting a protective effect of physical activity. However, this might also be because of reverse causality as asthmatics may be less likely to exercise regularly than non-asthmatics. The five longitudinal studies are more convincing in that respect as they all measured physical activity levels before asthma was diagnosed. The meta-analysis was not able to assess the independent contribution of physical inactivity and overweight to asthma development, which is important as they are closely

associated [21]. In this respect, the findings of Egan *et al.* in 1596 Norwegian adolescents are important. They showed that the presence of general or abdominal obesity is a risk factor for the development of asthma during 11 years follow-up after adjusting for current sports participation as a proxy for physical activity [9]. Another interesting observation is the association between asthma and television watching, which may be an indirect marker of physical inactivity. In a cross-sectional study in 20.016 children at 6–7 years of age, a high body weight, spending a lot of time watching television, and a salty diet each independently increased the risk of asthma [22]. The effect of television watching was also investigated in a longitudinal study in 3065 children who did not have symptoms of wheeze at an age of 3.5 years, but from whom 6% developed asthma at the age of 11.5 years, as demonstrated by a positive methacholine provocation test and children who watched television for more than two hours/day were almost twice as likely to develop asthma, irrespective of their BMI [23]. Different hypotheses have been put forward to explain the possible negative effects on asthma development [21,24]. First, physical inactivity may increase systemic and local airway inflammation [25], second, it may decrease mucociliary clearance and the patency of the bronchioles [21], and third, decreased deep inspiration and sigh rate during physical inactivity like television watching could result in a latch state of the smooth muscles and increased risk of bronchial hyperresponsiveness (BHR) [26].

Link between obesity and airway inflammation

Obesity is well known to be associated with a chronic low-grade systemic inflammation, as reflected by blood leukocytosis and increased serum levels of C-reactive protein [27,28]. Adipocytes produce and store several pro-inflammatory mediators such as leptin, tumor necrosis factor (TNF)a, monocyte chemotactic protein-1, and Interleukin (IL)-6, also called adipokines [29,30,31]. These Adipokines have the ability to modulate the adaptive and immune system in several ways including activation of T helper cells particularly those of the T helper 1 phenotype. In addition to the pleiotropic pro-inflammatory effects of TNFa and IL-6, leptin and monocyte chemotactic protein-are known to induce chemotaxis and activation of leukocytes and monocytes [32,33]. Furthermore, IL-6 has been implicated in the shift toward T helper 17 differentiation that has been observed in T cells from obese mice [34]. In obese individuals, adipose tissue derived dendritic cells, expressing high levels of IL-6 [35], have been shown to promote T helper 17 differentiation [36]. Of interest, T helper 17 cells have been associated with

neutrophilic airway inflammation in asthma [37]. Finally, increased blood levels of markers for oxidative stress have been reported in obese asthma patients [38]. These increased features of systemic inflammation and oxidative stress may also affect the type and severity of inflammatory process within the airways of patients with asthma [38]. Indeed, overweight and obese asthma patients have been reported to present with a different type of airway inflammation, with less eosinophils and more neutrophils in their induced sputum [3,39,40]. This is compatible with the findings by Haldar *et al.* [41] using a cluster analysis to identify an asthma subphenotype characterized by obese patients with an increased percentage of sputum neutrophils, high levels of symptoms, and poor responsiveness to treatment with inhaled or oral corticosteroids. Telenga *et al.* [3] also found obesity to be associated with a higher percentage of sputum neutrophils and a lower percentage of sputum eosinophils. Taken together, obesity may affect the type of airway inflammation in asthma leading to more neutrophils and less eosinophils in sputum. However, this contrasts with the findings from Desai *et al.* [42] investigating the association between obesity (BMI 30 kg/m²) and airways inflammation in both sputum and bronchial biopsies from patients with severe asthma. They did not find the number of blood or sputum eosinophils to be increased, yet found significantly higher IL-5 levels in sputum of obese asthmatics compared with both overweight (BMI 25–30 kg/m²) and lean (BMI <25 kg/m²) asthmatic controls. Interestingly, higher numbers of eosinophils were found in the airway walls of obese asthma patients as compared with the same control groups. This suggests a discrepancy between inflammatory cell findings in sputum and airway wall biopsies in obese and non-obese study participants with asthma. The latter was recently confirmed by van der Wiel *et al.* [43] in mild-to-moderate asthma patients. They found the percentage of sputum eosinophils to be lower in obese compared with non-obese asthma patients, which is compatible with the previously reported non-eosinophilic phenotype of obese asthma based on sputum analysis [3,39–41]. However, similar to the findings of Desai *et al.* [42] submucosal eosinophil numbers were found to be increased in obese compared with non-obese asthma patients [43]. The above-described findings show that, despite the absence of blood eosinophilia, eosinophilic airway inflammation can be present in obese asthma patients and possibly even to a higher extent than in non-obese asthmatics. However, sputum may not be the appropriate compartment to investigate this.

Mechanical effects of obesity

Spirometry, lung volumes, and airway resistance

Obesity has been associated with reduced lung function. An increased abdominal and thoracic adipose tissue mass inhibits an optimal inflation of the lungs. In line with this, several studies have reported a higher BMI to be associated with both a lower forced expiratory volume in 1 second (FEV_1) and a lower forced vital capacity (FVC) [44–46]. However, the effect was found to be small and even undetectable in some studies (figure 2) [3,47–49]. As both FEV_1 and FVC are similarly affected by obesity, the FEV_1/FVC ratio usually remains unaltered in obese asthmatics.

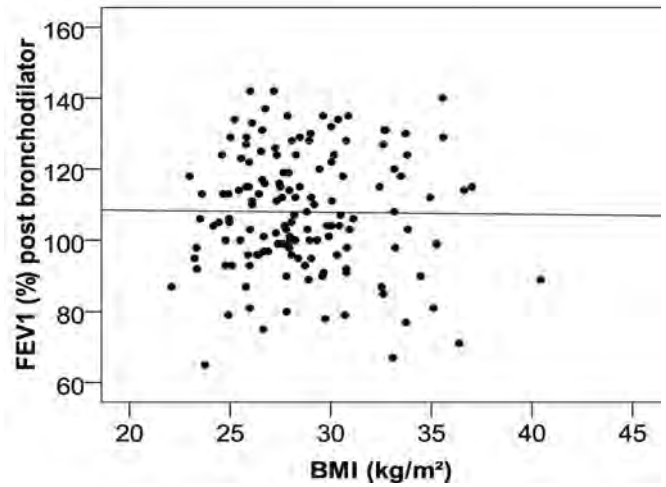

Figure 2: effects of BMI on FEV_1. This study found no significant correlation. (Pearson correlation coefficient: 0.027, P=0.41). FEV_1, forced expiratory volume in 1 second.
Reprinted with permission (Thijs W, et al. Respir Med. 2014 Feb;108(2):351-7).

Jones *et al.* [50] investigated how obesity affects lung volumes in study participants without obstructive or interstitial lung disease. Obesity was found to weakly affect the residual volume and total lung capacity, the decrease being approximately 10% in study participants with morbid obesity (BMI 40 kg/m²) compared with lean (BMI <25 kg/m²) controls. In contrast to the relatively small effect on residual volume, and total lung capacity, the impact of obesity on functional residual capacity and expiratory reserve volume (ERV) was found to be much larger with a clear dose–response relationship. As an example, the ERV was only 34% of the predicted normal value in study participants with morbid obesity (BMI 40 kg/m²; Figure 3). Importantly, the dramatic decrease of

ERV may cause morbidly obese study participants to perform tidal breathing at very low lung volumes. As a consequence, non-cartilaginous small airways are more likely to collapse at the end of expiration, leading to their cyclical opening and closure during tidal breathing. The latter renders obese study participants more prone to develop hyperinflation during bronchoconstriction [51,52]. In addition, these sequelae may damage the airway epithelium, thereby inducing pro-inflammatory response in the airways [53].

Bronchial hyperresponsiveness

The relationship between obesity and BHR has been the subject of debate with some studies reporting a significant association [11,54,55], whereas other studies found no relationship [3,56,57]. One very large study by Chinn *et al.* [58] investigating 11 277 adults from the European Community Survey II, reported that a higher BMI was associated with a more severe BHR measured with Provocative dose of methacholine causing a 20% drop in FEV_1 (PC_{20} methacholine) [58]. However, the magnitude of the effect reported in this study was small: an increase in BMI of 10 kg/m² would be needed to decrease the PC_{20} methacholine by only 0.3 doubling doses. Taken together, it can be concluded that obesity only weakly affects the presence and severity of BHR in asthma patients.

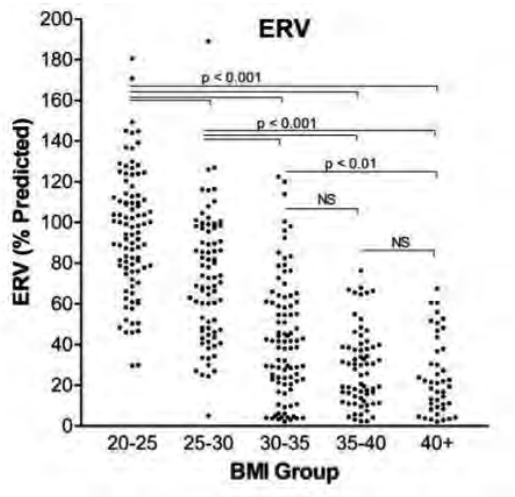

Figure 3: effects of BMI on expiratory reserve volume. Obesity has a dramatic and dose-dependent effect on the ERV such that study participants with morbid obesity perform tidal breathing at very low lung volumes close to their residual volume. ERV, expiratory reserve volume. Reproduced with permission (Jones RL, et al. Chest 2006; 130:827–833).

Obesity affects asthma symptoms and response to anti-inflammatory therapy

Obesity is associated with reduced asthma control and more frequent exacerbations in patients with asthma, even after adjusting for age, sex, and level of FEV_1 [59–62]. In addition, obese asthmatics are more difficult to control by anti-inflammatory treatment with ICS [3,48,49,63,64]. Anderson *et al.* [65] performed a post hoc analysis of a cross-over study investigating the efficacy of inhaled budesonide in 72 patients with asthma divided into two groups: lean (BMI <25 kg/m², n = 25) and overweight (BMI 25 kg/m², n = 47). Patients were treated for 4 weeks with either 200 mg/day or 800mg/day budesonide separated by a washout period of 1 – 2 weeks [65]. Although no differences with respect to change in FEV_1 and BHR were found between lean and overweight asthma patients, inhaled budesonide was less effective in improving symptoms in overweight asthma patients [65]. As budesonide also induced less cortisol suppression in overweight compared with lean asthma patients, it was suggested that airway geometric factors leading to a lower peripheral lung deposition may play a role in the reduced ICS treatment responsiveness [65]. In another study, Peters- Golden *et al.* [49] investigated how obesity affects treatment responsiveness to either inhaled beclomethasone 200mg twice daily or montelukast 10mg once daily in 3,073 patients with asthma. In lean asthma patients, inhaled beclomethasone improved the percentage of asthma control days to a higher extent than montelukast. However, overweight and obesity decreased treatment responsiveness to inhaled beclomethasone, whereas responsiveness to montelukast was not affected. As a consequence montelukast was found to be as effective as inhaled beclomethasone in overweight and obese asthma patients [49]. However, these findings are in contrast with those of Sutherland *et al.* [66] who performed a post hoc analysis in 1.052 asthma patients and found the ICS fluticasone proprionate to be more effective in improving FEV_1, peak-flow, beta-agonist use, and symptom scores than Montelukast not only in lean, but also in overweight and obese asthma patients. In a further study, Farah *et al.* [46] investigated the association between obesity and asthma symptoms before and after treatment with 1500 mg beclomethasone daily (or equivalent) in 49 asthma patients, a total of 14 out of 49 being overweight and 15 out of 49 obese. Although no correlation was found at baseline, a higher BMI strongly correlated with residual asthma symptoms that remained present despite intensive treatment with high doses of ICS for 3 months [Fig. 4] [46]. These findings suggest that both corticosteroid responsive and unresponsive factors contribute to the poorer asthma control generally observed in obese patients. The latter may be important, especially given the recent findings from

Gibeon *et al.* [67] comparing the clinical characteristics of obese (BMI 30) and non-obese (BMI 18–25) patients with severe asthma. Despite a similar degree of airflow obstruction and eosinophilic sputum inflammation, obese asthma patients more often received maintenance treatment with a high dose of oral prednisolone [67]. This approach is unlikely to improve corticosteroid unresponsive factors linked to reduced asthma control, but may lead to side-effects which can be quite severe, among others the fact that it drives insulin resistance and, consequently, obesity.

Effects of weight loss in obese asthma patients

Weight loss achieved by either caloric restriction and/or exercise has been shown to improve asthma symptoms and lung function [68–71]. Scott *et al.* [71] showed that even a modest weight loss of 5–10% improves asthma control as reflected by asthma control questionnaire scores. Although a larger weight loss did not further improve asthma control, it did induce further lung function improvements, particularly with respect to functional residual capacity and ERV values. In the study by Scott *et al.*, caloric restriction was more effective in reducing body weight than exercise alone.

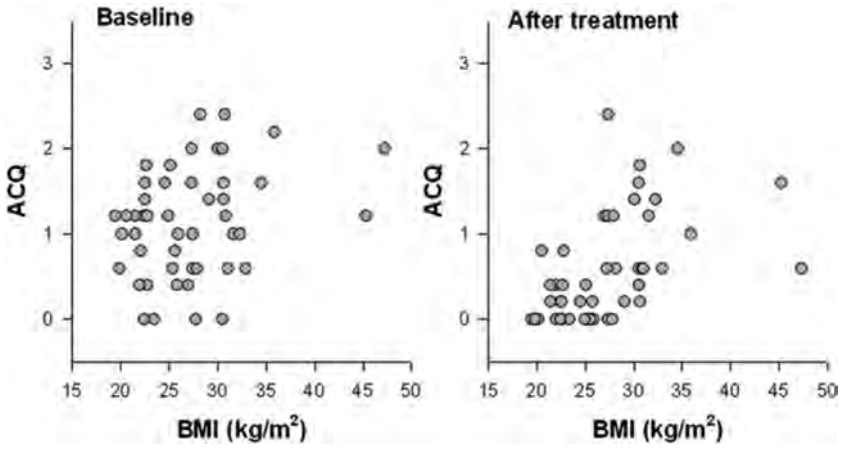

Figure 4: there was no correlation between the ACQ scores and BMI at baseline (Spearman correlation coefficient: 0.22, P=0.14). However, ACQ scores strongly correlated with BMI after 3 months of intensive treatment with a high dose inhaled corticosteroids (Spearman correlation coefficient: 0.58, P<0.001), suggesting that obesity contributes importantly to the corticosteroid-unresponsive component of symptoms in asthma patients. ACQ, asthma control questionnaire.
Reproduced with permission (Farah CS, et al. Chest. 2011 Sep;140(3):659-666).

Studies investigating the effects of bariatric surgery in morbidly obese asthma patients consistently report improvements of asthma control. In one retrospective study, 257 patients using asthma medication were followed up 1-year post-bariatric surgery. Among these 257 patients, 13/28 did not need oral corticosteroids any longer to control their asthma, whereas the overall use of ICS decreased from 50 to 30%. Importantly, patients who underwent laparoscopic gastric banding, which resulted in less weight loss than other surgical treatments, were significantly less likely to stop their oral or ICS. In addition to improvements of asthma control, bariatric surgery has been shown to improve small and large airway function and BHR [72-74]. Few studies have investigated the effects of weight loss on measures of airway inflammation. In a study by Dixon *et al.* [72] bariatric surgery did not improve airways inflammation as reflected by inflammatory cell numbers in bronchoalveolar lavage fluid. Van Huisstede *et al.* [74] investigated the effects of profound weight loss after bariatric surgery on lung function and on systemic inflammation as well as on inflammatory cell counts in bronchial biopsies in 27 asthmatics and 39 non-asthmatics with morbid obesity. As anticipated, improvements in symptoms and large and small airway function were observed both in obese study participants with and without asthma. In addition, BHR markedly improved in obese asthma patients after bariatric surgery and BHR (i.e., methacholine PC_{20} <1.8mg) could no longer be detected in 13 out of 25 patients despite lower doses ICS. Finally, bariatric surgery was found to decrease systemic inflammation and the number of mast cells in bronchial biopsies, whereas other inflammatory cell counts in bronchial biopsies did not change.

Asthma-related comorbidities and obesity

Comorbid conditions such as obstructive sleep apnea (OSA), gastroesophageal reflux disease (GERD), metabolic syndrome, and cardiovascular diseases are more prevalent in obese study participants and may also contribute to the clinical expression of asthma. Obesity is a well-known risk factor for OSA. This may have implications for asthma, as the presence of OSA has been associated with worse asthma control and its treatment with continuous positive airway pressure improves asthma symptoms, peak-flow, and BHR. On the other hand, it is important to understand that asthma itself is also a risk factor for OSA, irrespective of BMI. In a study by Julien *et al.* [75] OSA was found to be more frequently present in severe asthma (23 out of 26 patients) and moderate asthma (15 out of 26 patients) when compared with non-asthmatic controls (eight out

of 26) with a similar age and BMI. GERD is another frequently occurring comorbidity in asthma that is related to obesity [18] and poor asthma control. However, treatment of asymptomatic GERD with a proton-pump inhibitor did not improve asthma control even in a subgroup of obese asthma patients [76]. In addition, adjustment for both OSA and GERD did not change the asthma–obesity relationship In two large epidemiological studies [77,78]. Further, cardiopulmonary deconditioning is more frequently observed in obese than lean asthma patients [79]. Finally, insulin resistance or elevated blood glucose, one of the components of the metabolic syndrome, is another possible factor contributing to the asthma–obesity relationship. In a study by Brumpton *et al.* [80] an elevated fasting glucose or established diabetes was found to be associated with the presence of asthma even after adjustment for obesity. This is compatible with the findings of Thuesen *et al.* [81] showing insulin resistance to be associated with the development of asthma symptoms during a follow-up period of 5 years. Cardet *et al.* [82] showed that the association between insulin resistance and asthma is robust and remains present after adjusting for other components of the metabolic syndrome like hypertriglyceridemia, hypertension, hyperglycaemia, and systemic inflammation. The latter may be important, as it has been suggested that treatments targeting insulin resistance may be beneficial in obese asthma patients. In a recent retrospective study, Li *et al.* [83] found metformin, a drug that recovers peripheral insulin sensitization, to reduce the number of asthma exacerbations in obese patients with asthma and diabetes.

Conclusion

Obesity increases the risk for asthma development and affects its clinical expression toward a difficult-to-control phenotype. Although the mechanisms underlying the asthma–obesity relationship are not fully understood, several possible explanations have been put forward. First, obesity considerably reduces the ERV causing obese study participants to perform tidal breathing at low lung volumes, making them more susceptible to develop hyperinflation during bronchoconstriction. Second, obesity in asthma is associated with comorbidities such as OSAS and GERD, enhancing treatment complexity. Third, it affects the type and severity of the inflammatory process occurring in the airways in obese and overweight asthmatics characterized by more neutrophils and less eosinophils in sputum. Finally, it has been proposed that obesity is associated with a reduced corticosteroid treatment response. Nevertheless, obese asthma patients are often prescribed maintenance treatment with systemic corticosteroids. It is questionable whether this approach improves asthma control. To the opinion of the authors, systemic corticosteroid treatment should be avoided as much as possible even more in overweight and obese asthma patients, also because it further worsens obesity itself.

References

1. Dixon AE, Holguin F, Sood A, *et al.* An official American Thoracic Society workshop report: obesity and asthma. Proc Am Thorac Soc 2010; 7:325–335.
2. Mannino DM, Homa DM, Akinbami LJ, *et al.* Surveillance for asthma: United States, 1980-1999. MMWR Surveill Summ 2002; 51:1–13.
3. Telenga ED, Tideman SW, Kerstjens HA, *et al.* Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. Allergy 2012; 67:1060–1068.
4. Mosen DM, Schatz M, Magid DJ, *et al.* The relationship between obesity and asthma severity and control in adults. J Allergy Clin Immunol 2008; 122:507–511.
5. Rönmark E, Andersson C, Nystro¨m L, *et al.* Obesity increases the risk of incident asthma among adults. Eur Respir J 2005; 25:282–288.
6. Chen Y, Dales R, Jiang Y. The association between obesity and asthma is stronger in nonallergic than allergic adults. Chest 2006; 130:890–895.
7. Schachter LM, Salome CM, Peat JK, Woolcock AJ. Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness. Thorax 2001;56:4–8.
8. Guerra S, Sherrill DL, Bobadilla A, *et al.* The relation of body mass index to asthma, chronic bronchitis, and emphysema. Chest 2002; 122:1256–1263.
9. Egan KB, Ettinger AS, DeWan AT, *et al.* Longitudinal associations between asthma and general and abdominal weight status among Norwegian adolescents and young adults: the HUNT Study. Pediatr Obes 2015; 10:345–352.
10. Chen Y, Rennie D, Cormier Y, Dosman J. Sex specificity of asthma associated with objectively measured body mass index and waist circumference. Chest 2005; 128:3048–3054.
11. Hancox RJ, Milne BJ, Poulton R, *et al.* Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. Am J Respir Crit Care Med 2005; 171:440–445.
12. Schachter LM, Peat JK, Salome CM. Asthma and atopy in overweight children. Thorax 2003;58:1031–1035.
13. Bustos P, Amigo H, Oyarzu´n M, Rona RJ. Is there a causal relation between obesity and asthma? Evidence from Chile. Int J Obes (Lond) 2005;29:804–809.
14. Celedón JC, Palmer LJ, Litonjua AA, *et al.* Body mass index and asthma in adults in families of subjects with asthma in Anqing, China. Am J Respir Crit Care Med 2001; 164:1835–1840.
15. Appleton SL, Adams RJ, Wilson DH, *et al.* Central obesity is associated with nonatopic but not atopic asthma in a representative population sample. J Allergy Clin Immunol 2006; 118:1284–1291.
16. Brumpton B, Langhammer A, Romundstad P, *et al.* General and abdominal obesity and incident asthma in adults: the HUNT study. Eur Respir J 2013;41:323–329.
17. Von Behren J, Lipsett M, Horn-Ross PL, *et al.* Obesity, waist size and prevalence of current asthma in the California Teachers Study cohort. Thorax 2009; 64:889–893.
18. Pakhale S, Doucette S, Vandemheen K, *et al.* A comparison of obese and nonobese people with asthma: exploring an asthma-obesity interaction. Chest 2010; 137:1316–1323.
19. van Huisstede A, Castro Cabezas M, van de Geijn G, *et al.* Underdiagnosis and overdiagnosis of asthma in the morbidly obese. Respir Med 2013;107:1356–1364.
20. Ali Z, Ulrik CS. Obesity and asthma: a coincidence or a causal relationship? A systematic review. Respir Med 2013; 107:1287–1300.
21. Eijkemans M, Mommers M, Draaisma JM, *et al.* Physical activity and asthma: a systematic review and meta-analysis. PLoS One 2012; 7:e50775.
22. Corbo GM, Forastiere F, De Sario M, *et al.*, Sidria-2 Collaborative Group. Wheeze and asthma in children: associations with body mass index, sports, television viewing, and diet. Epidemiology 2008; 19:747–755.
23. Sherriff A, Maitra A, Ness AR, *et al.* Association of duration of television viewing in early childhood with the subsequent development of asthma. Thorax 2009; 64:321–325.
24. ten Hacken NH. Physical inactivity and obesity: relation to asthma and chronic obstructive pulmonary disease? Proc Am Thorac Soc 2009;6:663–667.
25. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology 2002; 13:561–568.
26. Lucas SR, Platts-Mills TA. Physical activity and exercise in asthma: relevance to etiology and treatment. J Allergy Clin Immunol 2005; 115:928–934.
27. Visser M, Bouter LM, McQuillan GM, *et al.* Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999; 282:2131–2135.
28. Ford ES. The metabolic syndrome and C-reactive protein, fibrinogen, and leukocyte count: findings from the Third National Health and Nutrition Examination Survey. Atherosclerosis 2003; 168:351–358.
29. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005; 115:911–919.
30. Xu H, Barnes GT, Yang Q, *et al.* Chronic inflammation in fat plays a crucial role in the development of obesity related insulin resistance. J Clin Invest 2003; 112:1821–1830.
31. Rastogi D, Fraser S, Oh J, *et al.* Inflammation, metabolic dysregulation, and pulmonary function among obese urban adolescents with asthma. Am J Respir Crit Care Med 2015; 191:149–160.

32 Zarkesh-Esfahani H, Pockley G, Metcalfe RA, *et al.* High-dose leptin activates human leukocytes via receptor expression on monocytes. J Immunol 2001;167:4593–4599.

33 Santos-Alvarez J, Goberna R, Sanchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. Cell Immunol 1999; 194:6–11.

34 Winer S, Paltser G, Chan Y, *et al.* Obesity predisposes to TH17 bias. Eur J Immunol 2009; 39:2629–2635.

35 Chen Y, Tian J, Tian X, *et al.* Adipose tissue dendritic cells enhances inflammation by prompting the generation of TH17 cells. PLoS One 2014;9:e92450.

36 Bertola A, Ciucci T, Rousseau D, *et al.* Identification of adipose tissue dendritic cells correlated with obesity-associated insulin-resistance and inducing TH17 responses in mice and patients. Diabetes 2012; 61:2238–2247.

37 Bullens DMA, Truyen E, Coteur L, *et al.* IL-17 mRNA in sputum of asthmatic patients: linking T cell driven inflammation and granulocytic influx? Respir Res 2006; 7:135.

38 Komakula S, Khatri S, Mermis J, *et al.* Body mass index is associated with reduced exhaled nitric oxide and higher exhaled 8-isoprostanes in asthmatics. Respir Res 2007; 8:32.

39 Scott HA, Gibson PG, Garg ML, *et al.* Airway inflammation is augmented by obesity and fatty acids in asthma. Eur Respir J 2011; 38:594–602.

40 van Veen IH, Ten Brinke A, Sterk PJ, *et al.* Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. Allergy 2008; 63:570–574.

41 Haldar P, Pavord ID, Shaw DE, *et al.* Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008; 178:218–224. Desai D, Newby C, Symon FA, *et al.* Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. Am J Respir Crit Care Med 2013; 188:657–663.

43 van der Wiel E, ten Hacken NH, van den Berge M, *et al.* Eosinophilic inflammation in subjects with mild-to-moderate asthma with and without obesity: disparity between sputum and biopsies. Am J Respir Crit Care Med 2014; 189:1281–1284.

44 Sutherland ER, Lehman EB, Teodorescu M, Wechsler ME; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Body mass index and phenotype in subjects with mild-to-moderate persistent asthma. J Allergy Clin Immunol 2009; 123:1328.e1–1334.e1.

45 Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. Arch Intern Med 2002; 162:1477–1481.

46 Farah CS, Kermode JA, Downie SR, *et al.* Obesity is a determinant of asthma control independent of inflammation and lung mechanics. Chest 2011; 140:659–666.

47 Thijs W, Alizadeh Dehnavi R, Hiemstra PS, *et al.* Association of lung function measurements and visceral fat in men with metabolic syndrome. Respir Med 2014; 108:351–357.

48 Camargo CA, Sutherland ER, Bailey W, *et al.* Effect of increased body mass index on asthma risk, impairment and response to asthma controller therapy in African Americans. Curr Med Res Opin 2010; 26:1629–1635.

49 Peters-Golden M, Swern A, Bird SS, *et al.* Influence of body mass index on the response to asthma controller agents. Eur Respir J 2006; 27: 495–503.

50 Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. Chest 2006; 130:827–833.

51 Salome CM, Munoz PA, Berend N, *et al.* Effect of obesity on breathlessness and airway responsiveness to methacholine in nonasthmatic subjects. Int J Obes (Lond) 2008; 32:502–509.

52 Deesomchok A, Fisher T, Webb KA, *et al.* Effects of obesity on perceptual and mechanical responses to bronchoconstriction in asthma. Am J Respir Crit Care Med 2010; 181:125–133.

53 Yalcin HC, Perry SF, Ghadiali SN. Influence of airway diameter and cell confluence on epithelial cell injury in an in vitro model of airway reopening. J Appl Physiol 2007; 103:1796–1807.

54 Litonjua AA, Sparrow D, Celedon JC, *et al.* Association of body mass index with the development of methacholine airway hyperresponsiveness in men: the Normative Aging Study. Thorax 2002; 57:581–585.

55 Ciprandi G, Pistorio A, Tosca M, *et al.* Body mass index, respiratory function and bronchial hyperreactivity in allergic rhinitis and asthma. Respir Med 2009;103:289–295.

56 Mansell AL, Walders N, Wamboldt MZ, *et al.* Effect of body mass index on response to methacholine bronchial provocation in healthy and asthmatic adolescents. Pediatr Pulmonol 2006; 41:434–440.

57 Holguin F, Bleecker ER, Busse WW, *et al.* Obesity and asthma: an association modified by age of asthma onset. J Allergy Clin Immunol 2011; 127:1486.e2–1493.e2.

58 Chinn S, Jarvis D, Burney P; European Community Respiratory Health Survey. Relation of bronchial responsiveness to body mass index in the ECRHS. European Community Respiratory Health Survey. Thorax 2002; 57:1028–1033.

59 Lavoie KL, Bacon SL, Labrecque M, *et al.* Higher BMI is associated with worse asthma control and quality of life but not asthma severity. Respir Med 2006; 100:648–657.

60 Kilic H, Oguzulgen IK, Bakir F, *et al.* Asthma in obese women: outcomes and factors involved. J Investig Allergol Clin Immunol 2011; 21:290–296.

61 Quinto KB, Zuraw BL, Poon KY, *et al.* The association of obesity and asthma severity and control in children. J Allergy Clin Immunol 2011; 128:964–969.

62 Kattan M, Kumar R, Bloomberg GR, *et al.* Asthma control, adiposity, and adipokines among inner-city adolescents. J Allergy Clin Immunol 2010;125:584–592.

63 Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. Respir Med 2007; 101:2240–2247.

64 Camargo CA Jr, Boulet LP, Sutherland ER, *et al.* Body mass index and response to asthma therapy: fluticasone propionate/salmeterol versus montelukast. J Asthma 2010; 47:76–82.

65 Anderson WJ, Lipworth BJ. Does body mass index influence responsiveness to inhaled corticosteroids in persistent asthma? Ann Allergy Asthma Immunol 2012; 108:237–242.

66 Sutherland ER, Camargo CA Jr, Busse WW, *et al.* Comparative effect of body mass index on response to asthma controller therapy. Allergy asthma Proc 2010; 31:20–25.

67 Gibeon D, Batuwita K, Osmond M, *et al.* Obesity-associated severe asthma represents a distinct clinical phenotype: analysis of the British Thoracic Society Difficult Asthma Registry Patient cohort according to BMI. Chest 2013; 143:406–414.

68 Stenius-Aarniala B, Poussa T, Kvarnstro¨m J, *et al.* Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. BMJ 2000; 320:827–832.

69 Johnson JB, Summer W, Cutler RG, *et al.* Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radic Biol Med 2007; 42:665–674.

70 Jensen ME, Gibson PG, Collins CE, *et al.* Diet-induced weight loss in obese children with asthma: a randomized controlled trial. Clin Exp Allergy 2013;43:775–784.

71 Scott HA, Gibson PG, Garg ML, *et al.* Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. Clin Exp Allergy 2013; 43:36–49.

72 Dixon AE, Pratley RE, Forgione PM, *et al.* Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. J Allergy Clin Immunol 2011; 128:508.e1–515-e.2.

73 Boulet LP, Turcotte H, Martin J, *et al.* Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. Respir Med 2012;106:651–660.

74 van Huisstede A, Rudolphus A, Castro Cabezas M, *et al.* Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma. Thorax 2015; 70:659–667.

75 Julien JY, Martin JG, Ernst P, *et al.* Prevalence of obstructive sleep apneahypopnea in severe versus moderate asthma. J Allergy Clin Immunol 2009;124:371–376.

76 American Lung Association Asthma Clinical Research Centers. Mastronarde JG, Anthonisen NR, Castro M, *et al.* Efficacy of esomeprazole for treatment of poorly controlled asthma. N Engl J Med 2009; 360:1487–1499.

77 Dixon AE, Clerisme-Beaty EM, Sugar EA, *et al.* Effects of obstructive sleep apnea and gastroesophageal reflux disease on asthma control in obesity. J Asthma 2011; 48:707–713.

78 Teodorescu M, Polomis DA, Hall SV, *et al.* Association of obstructive sleep apnea risk with asthma control in adults. Chest 2010; 138:543–550.

79 Shim YM, Burnette A, Lucas S, *et al.* Physical deconditioning as a cause of breathlessness among obese adolescents with a diagnosis of asthma. PLoS One 2013; 8:e61022.

80 Brumpton BM, Camargo CA, Romundstad PR, *et al.* Metabolic syndrome and incidence of asthma in adults: the HUNT study. Eur Respir J 2013;42:1495–1502.

81 Thuesen BH, Husemoen LL, Hersoug LG, *et al.* Insulin resistance as a predictor of incident asthma-like symptoms in adults. Clin Exp Allergy 2009; 39:700–707.

82 Cardet JC, Ash S, Kusa T, *et al.* Insulin resistance modifies the association between obesity and current asthma in adults. Eur Respir J 2016; 48:403–410.

83 Li CY, Erickson SR, Wu CH. Metformin use and asthma outcomes among patients with concurrent asthma and diabetes. Respirology 2016; 21:1210–1218.