Morbid obesity and asthma - co-morbidity or causal relationship?

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TABLE OF CONTENTS

1

General introduction and outline of the thesis

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

General introduction

Obesity is currently a major health problem and is developing into a global epidemic. Obesity is classified by the Body Mass Index (BMI) (table 1) and is defined as abnormal or excessive fat accumulation which can cause health problems. The World Health Organisation's (WHO) latest projections indicate that, globally in 2005, approximately 1.6 billion adults (age 15+) were overweight, and at least 400 million adults were obese. The WHO further predicts that - by 2015- approximately 2.3 billion adults will be overweight and more than 700 million will be obese. High body mass index has overtaken tobacco smoking as the most costly and detrimental preventable cause of deadly diseases in the United States[1].

Table 1 Body Mass Index classification

BMI (kg/m^2)	Classification
<18.5	Underweight
18.5-25	Normal weight
25-30	Overweight
30-40	Obesity
>40	Morbid Obesity

The prevalence and incidence of asthma has increased over the recent decades[2, 3]. Besides an improved awareness of the disease, there are several other explanations for the increased asthma prevalence, such as decreased exposure to microbial products, changes in microbiota, increased exposure to air pollution and tobacco smoke, a change in diet and obesity[3]. As the incidence and prevalence of obesity have increased concurrently with the incidence and prevalence of asthma (as shown in Figure 1 for the Netherlands), this is suggestive for a possible link between obesity and asthma[4, 5]. The observation that asthma symptoms decrease after weight loss with either bariatric surgery or low caloric diet supports a causal relationship between obesity and asthma[5]. Moreover, obese patients with persistent asthma have significantly worse asthma-related quality of life[6], less asthma control[7, 8], more severe disease[9-12], and more asthma-related hospital admissions than asthma patients with a normal BMI. As asthma is a heterogeneous disease, with different underlying disease processes, recognizable clusters of demographic, clinical and/or pathophysiological characteristics are called asthma phenotypes[13]. Asthma with obesity is one of these recognized phenotypes.

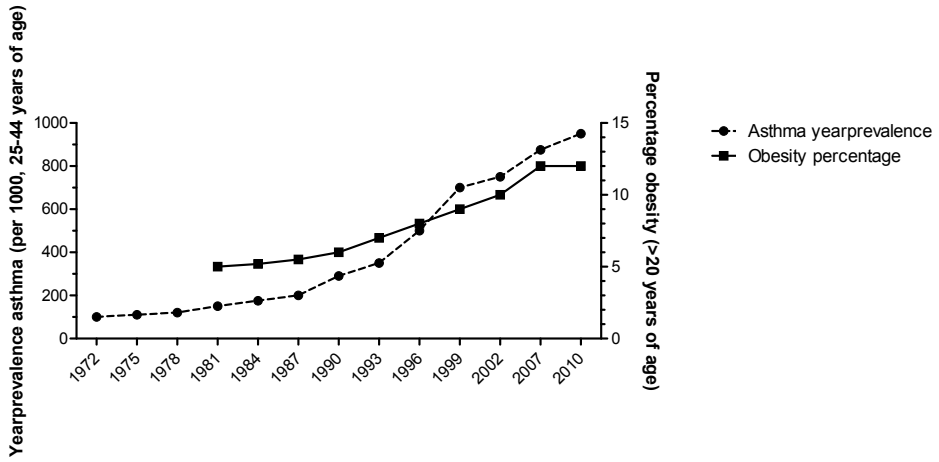

Figure 1 Temporal trends of obesity and asthma in the Netherlands

Temporal trends in the prevalence of obesity in adults and asthma in the Netherlands. The dotted line represents the prevalence of asthma, while the solid line represents the prevalence of obesity. Asthma year prevalence is standardized to population of the Netherlands in 2010 and is index-linked to 1992 (source CMR-Nijmegen). Obesity data are standardized to age- and gender distribution of 1981 (source CBS statline, 2013).

Diagnosis of asthma in the morbidly obese

According to the latest Global Initiative for Asthma (GINA) definition of 2014, asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation[13].

GINA guidelines advise that asthma diagnosis should be based on both the presence of symptoms and objective measurements of variable expiratory airflow limitation[13]. However, in daily practice the diagnosis of asthma is mainly based on symptoms, and spirometry or provocation tests are not always performed[14]. Since obese subjects report more dyspnea than non-obese subjects[15, 16], it might be that they get mislabelled as asthma (overdiagnosis). Inevitably, any overdiagnosis may lead to inappropriate treatment[14], with increased risk of side-effects and increased costs[17].

Many epidemiological studies concerning obesity and asthma have used physician-diagnosed asthma without confirmation by pulmonary function tests. This implies, as discussed earlier, reasonable doubt as to the accuracy of the diagnosis of asthma. Several studies report that the diagnosis of asthma could be revisited after extensive testing in 30% of physician-diagnosed asthma[18-20], even after stopping with asthma medication[21]. On the other hand, missing the diagnosis of asthma in the obese population is also an important aspect. Impaired perception of dyspnea is thought to play a role especially in severe asthma[22, 23], and poor perception of airflow obstruction may lead

to under-treatment of asthma[24, 25]. All the recent studies investigating overdiagnosis of asthma in the obese[20, 21, 26] initially used selected subjects with asthma, and therefore did not take into account obese patients with so far undetected asthma. Therefore, only limited information is available about the underdiagnosis of asthma in the obese.

Bronchial and systemic inflammation in the morbidly obese

Obesity and asthma relationship

The mechanisms underlying the relationship between asthma and obesity are unclear. In previous reviews concerning the relationship between obesity and asthma, five hypotheses were suggested (figure 2)[27].

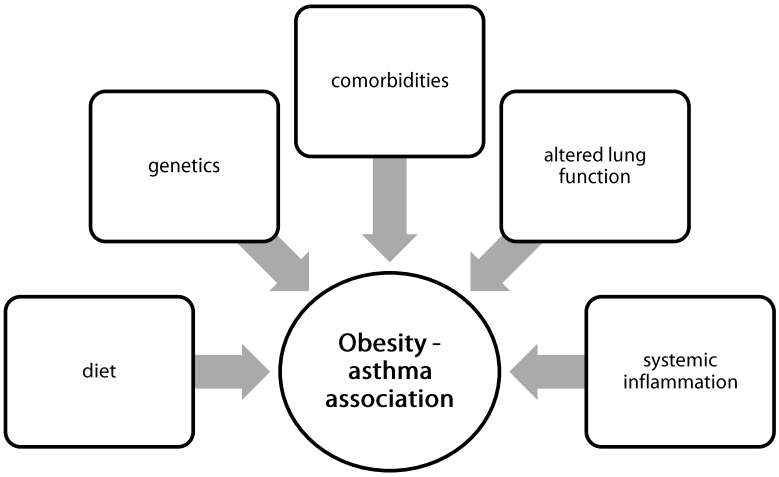

Figure 2 Explaining the obesity-asthma association

First, the diet of obese people consists of food with less nutritional value, fewer vitamins and more fat. A high amount of fat intake is associated with asthma[28]. Mineral deficiencies such as zinc- and magnesium deficiencies are associated with asthma and bronchial hyperreactivity (BHR)[29]. Second, asthma and obesity may share the same genetic risk factors. In a large-scale study among 1384 twins, a strong association between asthma and BMI was found[30]. The third hypothesis is that shared co-morbidities link these diseases. Obesity is a risk factor for gastro-oesophageal reflux disease (GERD) which, in turn, is a risk factor for asthma[31]. Another example is Obstructive Sleep Apnoea Syndrome (OSAS); the prevalence of OSAS is higher in severe asthma patients as well as in obese patients[32]. Fourth, obesity may influence lung function parameters. Typically, obesity causes a modest reduction in total lung capacity (TLC), and a larger reduction in functional residual capacity (FRC) (figure 3)[33].

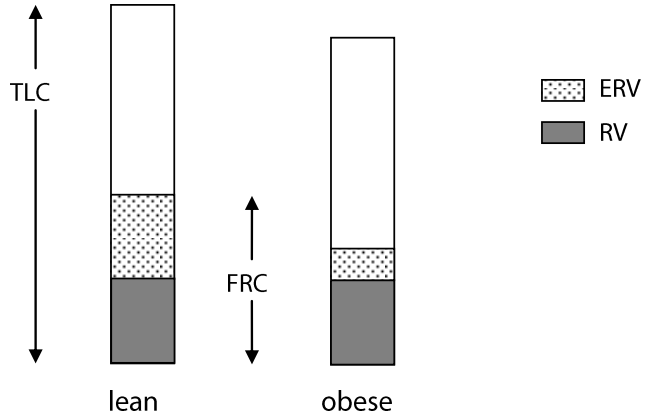

Figure 3. Altered lung function in obesity
Obesity leads to alternations of lung volumes. ERV: expiratory reserve volume; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity

The fifth hypothesis suggests that systemic inflammation may lead to asthma by means of fat-tissue derived adipokines. Obesity is considered to be a state of chronic low-grade systemic inflammation, characterized by an imbalance of pro- and anti-inflammatory proteins derived from adipocytes. Fat tissue was traditionally seen as an organ for storage of energy, however, it is now considered to act as an endocrine organ. The fat tissue is a source of bioactive peptides and proteins, which are called adipokines[34]. Examples of adipokines are leptin, adiponectin and resistin. Also interleukin (IL)-6 and TNF-α, produced by macrophages in the fat tissue, play a role.

Leptin (Greek leptos, thin) is secreted by fat tissue and causes the feeling of saturation and increases the metabolism. Moreover, leptin influences the T-cell response and stimulates the proliferation of T-helper cells, which causes increased production of pro-inflammatory cytokines[35]. Adiponectin is an insulin-regulating hormone. It also has anti-inflammatory effects: it decreases the production of pro-inflammatory cytokines and it increases the production of IL-10 and IL-1β. The assumption is that inflammatory mediators from the fat tissue enter the systemic circulation, and find their way to the lung tissue, where they may cause or intensify airway inflammation[36].

Systemic inflammation in the morbidly obese

The increasing prevalence of obesity may result in development of the metabolic syndrome. Metabolic syndrome is defined by a cluster of cardiometabolic risk factors characterized by abdominal obesity, insulin resistance and chronic systemic inflammation[37].

For components of the metabolic syndrome, such as hypertension[38], type 2 diabetes mellitus[39, 40], low-density lipoprotein cholesterol[41] and overall obesity[42] positive as-

sociations with lung function impairment have been reported. In recent large cohort studies it has been shown that there is also a relationship between metabolic syndrome and lung function impairment[43-45]. Data on the association between lung function impairment and the metabolic syndrome in the morbidly obese are limited.

The mechanisms underlying the relationship between the metabolic syndrome and impaired lung function are unclear. The relationship might be explained by the chronic low-grade systemic inflammation that is associated with obesity. One hypothesis is that this low-grade systemic inflammation causes inflammation in the lungs, and hence lung function impairment (figure 4).

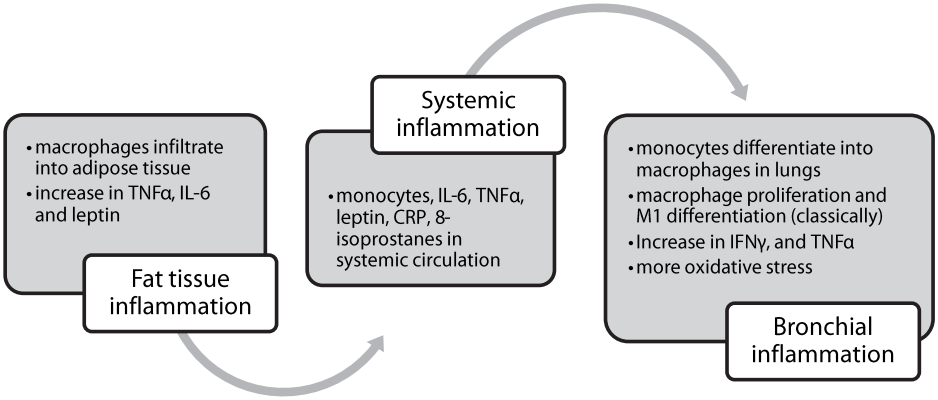

Figure 4 Inflammatory mechanism linking obesity and asthma
Inflammatory mechanisms linking obesity to asthma (adapted from Lugogo[46])

Bronchial inflammation in the morbidly obese

As stated previously, asthma is a chronic inflammatory disorder of the airways. The systemic inflammation, known to be present in the morbidly obese, may spill over into the lungs, and cause local inflammation in the airways, and thereby asthma. Indeed, asthma in the obese has been described as a specific phenotype, with a high symptom expression and late onset of symptoms[47, 48]. Typical allergic asthma is characterized by airway sputum eosinophilia and increased exhaled nitric oxide. Several studies in obese patients with asthma have shown an inverse relationship between BMI and exhaled nitric oxide and sputum eosinophilia[49-51]. Airway neutrophilia has been reported in obese asthmatic women as compared to obese controls and lean asthmatics[52]. There is however, some discrepancy in the literature concerning the nature of bronchial inflammation in obese asthmatics. While some research groups show increased sputum neutrophil counts[52, 53], others report no relationship between obesity and neutrophilic airway inflammation[50, 51, 54]. All aforementioned studies in obese asthmatics investigated induced sputum or bronchial alveolar lavage cell counts, which may not fully reflect tissue inflammation.

Bariatric surgery

Bariatric surgery procedures affect weight loss through two mechanisms: malabsorption and restriction. In the Sint Franciscus Gasthuis[55] two different bariatric surgery procedures are performed: the gastric sleeve resection and the (Roux-and Y) gastric bypass surgery. Sleeve gastrectomy is a partial gastrectomy, in which the majority of the greater curvature of the stomach is removed[56], and is thereby a restrictive method. During the gastric bypass surgery a small proximal gastric pouch is divided and separated from the distal stomach and anastomosed to a Roux limb of small bowel 75 to 150 cm in length[56] (figure 5). This is a combination of a restrictive and malabsorptive procedure.

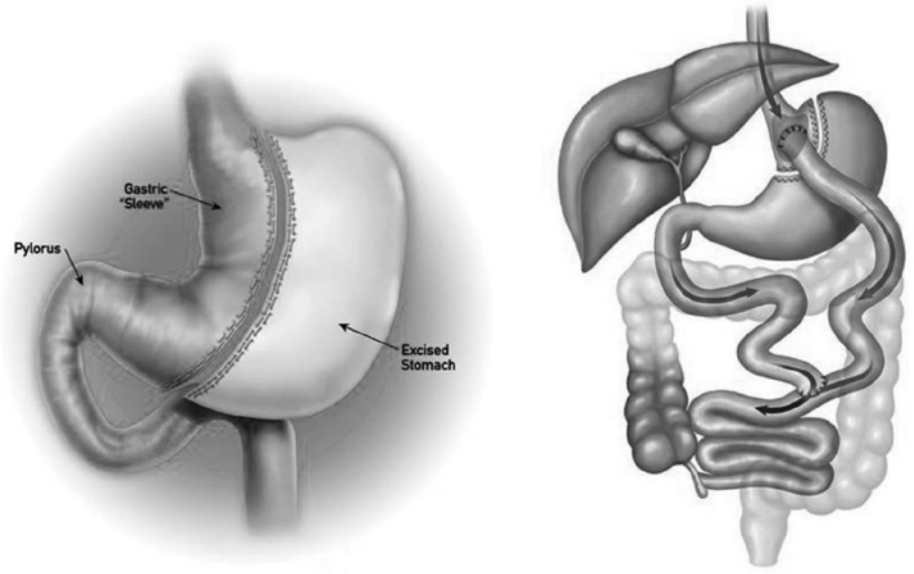

Figure 5 Gastric sleeve resection and gastric bypass surgery

Complications of bariatric surgery

In line with the epidemic of obesity, the number of bariatric surgery procedures being performed is increasing every year, with a 22-fold increase between 1996 and 2008[57]. The postoperative morbidity rate after bariatric surgery is about 5%. In a large cohort study it was shown that postoperative pneumonia and respiratory failure, despite being infrequent complications of bariatric surgery, account for one fifth of the morbidity. Moreover, these complications are also associated with increased mortality[58] and represent the largest attributable costs of all complications[59]. Since the surgery is elective and complications are difficult to treat in this group of morbidly obese patients, the prevention of complications of bariatric surgery is of great importance. Obesity is found to be a risk factor for the development of postoperative pulmonary complications after

abdominal surgery[60]. Obesity-related co-morbidities – such as asthma[61] - may predispose obese patients to postoperative complications.

Current guidelines do not indicate pulmonary function testing in patients without evidence of pre-existing lung disease who are evaluated for non-thoracic surgical procedures. However, whether this is also true for morbidly obese is unclear. Spirometry could identify patients who are at risk for complications, although this is not the current consensus[62]. The guidelines state that spirometry is only mandatory in patients who are heavy smokers, or have complaints of dyspnea or cough[63]. However, there is a poor correlation between the presence of symptoms and lung function measurements[64] in the general population, but also among the morbidly obese.

Bariatric surgery in the management of asthma

A recent position paper on weight loss interventions in asthma[65] concluded that the evidence of benefits from weight reduction on asthma outcomes is weak. They included studies with dietary interventions, including the only randomized controlled trial by Stenius[66]. Besides effect on asthma outcomes, weight loss from dietary interventions also have been associated with reduction in markers of systemic inflammation[67, 68]. However, in the morbidly obese is has been shown that bariatric surgery leads to more and persistent weight loss in contrast to dietary weight loss[69]. So it is to be expected that weight loss by bariatric surgery has a greater and prolonged effect on asthma.

To our knowledge only six prospective studies have been published in which the effects of bariatric surgery on obese asthmatic patients have been evaluated[70-75]. These six studies conclude that airway responsiveness, lung volumes and asthma control do markedly improve with weight loss following bariatric surgery in severely obese asthmatic patients. However, the numbers of included subjects were small in all six studies. Furthermore, they either lacked (follow-up of) a non-asthmatic control group of subjects with bariatric surgery[70, 71, 73, 75], or they lacked a non-intervention control group[71, 72, 74, 75].

Outline / aim of the thesis

The aim of the thesis is threefold. First, we investigated whether not only overdiagnosis but also underdiagnosis of asthma is present in an obese population. Secondly, we studied the following research questions:

- Is bronchial inflammation present in obese asthmatics?
- Is there a relationship between bronchial inflammation in obese asthmatics and obesity-associated low-grade systemic inflammation?

Finally, we studied the effect of bariatric surgery on asthma symptoms, lung function and bronchial and systemic inflammation.

This thesis consists of three parts. Part A describes in **chapter 2** the complex diagnosis of asthma in the morbidly obese, and especially focuses on underdiagnosis and overdiagnosis of asthma in this patient group. Part B investigates bronchial and systemic inflammation. It starts in **chapter 3** with a review on the association between obesity and asthma, where the metabolic syndrome – as state of systemic inflammation - is mentioned as possible explanation for the association between obesity and asthma. In **chapter 4** systemic inflammation and the metabolic syndrome and impaired lung function in morbidly obese subjects are discussed. This is followed by **chapter 5**, in which the presence and possible relationship between bronchial and systemic inflammation in morbidly obese asthma subjects are discussed. Part C focuses on bariatric surgery, first pulmonary function testing and complications of bariatric surgery are discussed in **chapter 6**. In **chapter 7** the effect of bariatric surgery on asthma is described. And finally, in **chapter 8**, a summary and general discussion of these studies is presented.

REFERENCES

1. Cawley J, Meyerhoefer C. The medical care costs of obesity: an instrumental variables approach. *J Health Econ* 2013;31(1):219-30.
2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31(1):143-78.
3. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355(21):2226-35.
4. Chinn S. Asthma and obesity: where are we now? *Thorax* 2003;58(12):1008-10.
5. Camargo CA, Jr., Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;159(21):2582-8.
6. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med* 2006;100(4):648-57.
7. Saint-Pierre P, Bourdin A, Chanez P, Daures JP, Godard P. Are overweight asthmatics more difficult to control? *Allergy* 2006;61(1):79-84.
8. Clerisme-Beaty EM, Karam S, Rand C, Patino CM, Bilderback A, Riekert KA, Okelo SO, Diette GB. Does higher body mass index contribute to worse asthma control in an urban population? *J Allergy Clin Immunol* 2009;124(2):207-12.
9. Taylor B, Mannino D, Brown C, Crocker D, Twum-Baah N, Holguin F. Body mass index and asthma severity in the National Asthma Survey. *Thorax* 2008;63(1):14-20.
10. Mosen DM, Schatz M, Magid DJ, Camargo CA, Jr. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol* 2008;122(3):507-11 e6.
11. Akerman MJ, Calacanis CM, Madsen MK. Relationship between asthma severity and obesity. *J Asthma* 2004;41(5):521-6.
12. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005;171(4):334-9.
13. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014. *Available from: http://www.ginasthma.org/*. 2014.
14. Lucas AE, Smeenk FW, Smeele IJ, van Schayck CP. Overtreatment with inhaled corticosteroids and diagnostic problems in primary care patients, an exploratory study. *Fam Pract* 2008;25(2):86-91.
15. Pakhale S, Doucette S, Vandemheen K, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Aaron SD. A comparison of obese and nonobese asthmatics: Exploring an asthma-obesity interaction. *Chest* 2010;137(6):1316-1323.
16. Babb TG, Ranasinghe KG, Comeau LA, Semon TL, Schwartz B. Dyspnea on exertion in obese women: association with an increased oxygen cost of breathing. *Am J Respir Crit Care Med* 2008; 178(2):116-23.
17. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, FitzGerald JM. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
18. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct? *Fam Pract* 1999;16(2):112-6.
19. LindenSmith J, Morrison D, Deveau C, Hernandez P. Overdiagnosis of asthma in the community. *Can Respir J* 2004;11(2):111-6.
20. Scott S, Currie J, Albert P, Calverley P, Wilding JP. Risk of mis-diagnosis, Health related Quality of Life and Body Mass Index in Overweight Patients with doctor diagnosed asthma. *Chest* 2012; 141(3):616-24.

21. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Doucette S, Fergusson D. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179(11):1121-31.
22. Veen JC, Smits HH, Ravensberg AJ, Hiemstra PS, Sterk PJ, Bel EH. Impaired perception of dyspnea in patients with severe asthma. Relation to sputum eosinophils. *Am J Respir Crit Care Med* 1998; 158(4):1134-41.
23. Bijl-Hofland ID, Cloosterman SG, Folgering HT, Akkermans RP, van Schayck CP. Relation of the perception of airway obstruction to the severity of asthma. *Thorax* 1999;54(1):15-19.
24. Boulet LP, Leblanc P, Turcotte H. Perception scoring of induced bronchoconstriction as an index of awareness of asthma symptoms. *Chest* 1994;105(5):1430-3.
25. van den Toorn LM, Overbeek SE, Prins JB, Hoogsteden HC, De Jongste JC. Dyspnoea perception during clinical remission of atopic asthma. *Eur Respir J* 2002;19(6):1047-50.
26. Luks VP, Vandemheen KL, Aaron SD. Confirmation of asthma in an era of overdiagnosis. *Eur Respir J* 2010;36(2):255-60.
27. Boulet LP. Asthma and obesity. *Clin Exp Allergy* 2013;43(1):8-21.
28. Weiss ST. Obesity: insight into the origins of asthma. *Nat Immunol* 2005;6(6):537-9.
29. Tantisira KG, Weiss ST. Complex interactions in complex traits: obesity and asthma. *Thorax* 2001; 56 Suppl 2:ii64-73.
30. Hallstrand TS, Fischer ME, Wurfel MM, Afari N, Buchwald D, Goldberg J. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. *J Allergy Clin Immunol* 2005; 116(6):1235-41.
31. Kiljander TO, Harding SM, Field SK, Stein MR, Nelson HS, Ekelund J, Illueca M, Beckman O, Sostek MB. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2006;173(10):1091-7.
32. Julien JY, Martin JG, Ernst P, Olivenstein R, Hamid Q, Lemiere C, Pepe C, Naor N, Olha A, Kimoff RJ. Prevalence of obstructive sleep apnea-hypopnea in severe versus moderate asthma. *J Allergy Clin Immunol* 2009;124(2):371-6.
33. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med* 2006;174(2): 112-9.
34. Ronti T, Lupattelli G, Mannarino E. The endocrine function of adipose tissue: an update. *Clin Endocrinol (Oxf)* 2006;64(4):355-65.
35. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* 1998;394(6696): 897-901.
36. Beuther DA. Obesity and asthma. *Clin Chest Med* 2009;30(3):479-88.
37. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109(3):433-8.
38. Selby JV, Friedman GD, Quesenberry CP, Jr. Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. *Am J Epidemiol* 1990; 131(6):1017-27.
39. Ford ES, Mannino DM. Prospective association between lung function and the incidence of diabetes: findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Diabetes Care* 2004;27(12):2966-70.

40. Yeh HC, Punjabi NM, Wang NY, Pankow JS, Duncan BB, Cox CE, Selvin E, Brancati FL. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* 2008;31(4):741-6.
41. Cirillo DJ, Agrawal Y, Cassano PA. Lipids and pulmonary function in the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2002;155(9):842-8.
42. Bottai M, Pistelli F, Di Pede F, Carrozzi L, Baldacci S, Matteelli G, Scognamiglio A, Viegi G. Longitudinal changes of body mass index, spirometry and diffusion in a general population. *Eur Respir J* 2002;20(3):665-73.
43. Leone N, Courbon D, Thomas F, Bean K, Jego B, Leynaert B, Guize L, Zureik M. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med* 2009;179(6):509-16.
44. Lin WY, Yao CA, Wang HC, Huang KC. Impaired lung function is associated with obesity and metabolic syndrome in adults. *Obesity* 2006;14(9):1654-61.
45. Naveed B, Weiden MD, Kwon S, Gracely EJ, Comfort AL, Ferrier N, Kasturiarachchi KJ, Cohen HW, Aldrich TK, Rom WN, Kelly K, Prezant DJ, Nolan A. Metabolic syndrome biomarkers predict lung function impairment: a nested case-control study. *Am J Respir Crit Care Med* 2012;185(4):392-9.
46. Lugogo NL, Bappanad D, Kraft M. Obesity, metabolic dysregulation and oxidative stress in asthma. *Biochim Biophys Acta* 2011;1810(11):1120-6.
47. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178(3):218-24.
48. Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, Stream AR, Fahy JV. Cluster analysis of obesity and asthma phenotypes. *PLoS One* 2012;7(5):e36631.
49. van Veen IH, Ten Brinke A, Sterk PJ, Rabe KF, Bel EH. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. *Allergy* 2008;63(5):570-4.
50. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? *Chest* 2008; 134(2):317-23.
51. Sutherland TJ, Cowan JO, Young S, Goulding A, Grant AM, Williamson A, Brassett K, Herbison GP, Taylor DR. The association between obesity and asthma: interactions between systemic and airway inflammation. *Am J Respir Crit Care Med* 2008;178(5):469-75.
52. Scott HA, Gibson PG, Garg ML, Wood LG. Airway Inflammation is Augmented by Obesity and Fatty Acids in Asthma. *Eur Respir J* 2011;38(3):594-602.
53. Telenga ED, Tideman SW, Kerstjens HA, Hacken NH, Timens W, Postma DS, van den Berge M. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. *Allergy* 2012;67(8):1060-8.
54. Todd DC, Armstrong S, D'Silva L, Allen CJ, Hargreave FE, Parameswaran K. Effect of obesity on airway inflammation: a cross-sectional analysis of body mass index and sputum cell counts. *Clin Exp Allergy* 2007;37(7):1049-54.
55. Elte JW, Castro Cabezas M, Vrijland WW, Ruseler CH, Groen M, Mannaerts GH. Proposal for a multidisciplinary approach to the patient with morbid obesity: the St. Franciscus Hospital morbid obesity program. *Eur J Intern Med* 2008;19(2):92-8.
56. Gilbert EW, Wolfe BM. Bariatric surgery for the management of obesity: state of the field. *Plast Reconstr Surg* 2012;130(4):948-54.
57. Buchwald H, Oien DM. Metabolic/bariatric surgery Worldwide 2008. *Obes Surg* 2009;19(12):1605-11.
58. Gupta PK, Gupta H, Kaushik M, Fang X, Miller WJ, Morrow LE, Armour-Forse R. Predictors of pulmonary complications after bariatric surgery. *Surg Obes Relat Dis* 2011;8(5):574-81.

59. Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA, Jr. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. *J Am Coll Surg* 2004;199(4):531-7.
60. Brooks-Brunn JA. Predictors of postoperative pulmonary complications following abdominal surgery. *Chest* 1997;111(3):564-71.
61. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;175(7):661-6.
62. Smetana GW. Postoperative pulmonary complications: an update on risk assessment and reduction. *Cleve Clin J Med* 2009;76 Suppl 4:S60-5.
63. Chetta A, Tzani P, Marangio E, Carbognani P, Bobbio A, Olivieri D. Respiratory effects of surgery and pulmonary function testing in the preoperative evaluation. *Acta Biomed* 2006;77(2):69-74.
64. Kerstjens HA, Brand PL, de Jong PM, Koeter GH, Postma DS. Influence of treatment on peak expiratory flow and its relation to airway hyperresponsiveness and symptoms. The Dutch CNSLD Study Group. *Thorax* 1994;49(11):1109-15.
65. Moreira A, Bonini M, Garcia-Larsen V, Bonini S, Del Giacco SR, Agache I, Fonseca J, Papadopoulos NG, Carlsen KH, Delgado L, Haahtela T. Weight loss interventions in asthma: EAACI evidence-based clinical practice guideline (part I). *Allergy*;68(4):425-39.
66. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *Bmj* 2000;320(7238):827-32.
67. Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, Giugliano D. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *Jama* 2003;289(14):1799-804.
68. Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, Vidal H, Hainque B. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *J Clin Endocrinol Metab* 2000;85(9):3338-42.
69. Kushner RF. Weight loss strategies for treatment of obesity. *Prog Cardiovasc Dis* 2014;56(4):465-72.
70. Maniscalco M, Zedda A, Faraone S, Cerbone MR, Cristiano S, Giardiello C, Sofia M. Weight loss and asthma control in severely obese asthmatic females. *Respir Med* 2008;102(1):102-8.
71. Dixon AE, Pratley RE, Forgione PM, Kaminsky DA, Whittaker-Leclair LA, Griffes LA, Garudathri J, Raymond D, Poynter ME, Bunn JY, Irvin CG. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011;128(3):508-15 e1-2.
72. Lombardi C, Gargioni S, Gardinazzi A, Canonica GW, Passalacqua G. Impact of bariatric surgery on pulmonary function and nitric oxide in asthmatic and non-asthmatic obese patients. *J Asthma* 2011;48(6):553-7.
73. Boulet LP, Turcotte H, Martin J, Poirier P. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respir Med* 2012;106(5):651-60.
74. Al-Alwan A, Bates JH, Chapman DG, Kaminsky DA, DeSarno MJ, Irvin CG, Dixon AE. The nonallergic asthma of obesity. A matter of distal lung compliance. *Am J Respir Crit Care Med* 2014;189(12):1494-502.
75. Sideleva O, Suratt BT, Black KE, Tharp WG, Pratley RE, Forgione P, Dienz O, Irvin CG, Dixon AE. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. *Am J Respir Crit Care Med* 2012;186(7):598-605.

PART A

DIAGNOSIS OF ASTHMA IN THE MORBIDLY OBESE

2

Underdiagnosis and overdiagnosis of asthma in the morbidly obese

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ABSTRACT

Background: The prevalence of obesity and asthma has increased concurrently over the last decades, suggesting a link between obesity and asthma. However, asthma might not be adequately diagnosed in this population.

Aim: To investigate whether not only overdiagnosis but also underdiagnosis of asthma is present in an obese population.

Methods: Morbidly obese subjects with or without physician-diagnosed asthma were recruited from a pre-operative screening programme for bariatric surgery, and were characterized using an extensive diagnostic algorithm.

Results: 473 subjects were screened; 220 met inclusion criteria, and 86 agreed to participate. Among the 32 participating subjects who had a physician diagnosis of asthma, reversible airway obstruction and/or bronchial hyperresponsiveness could only be detected in 19 patients (59%, 95%CI [0.41-0.76]), whereas in 13 patients (41%, 95%CI [0.24-0.50]) the diagnosis of asthma could not be confirmed (overdiagnosis). In contrast, in the remaining 54 patients, 17 (31%, 95% CI [0.20-0.46]) were newly diagnosed with asthma (underdiagnosis).

Conclusion: Besides overdiagnosis, there is also substantial underdiagnosis of asthma in the morbidly obese. Symptoms could be incorrectly ascribed to either obesity or asthma, and therefore also in the morbidly obese the diagnosis of asthma should also be based on pulmonary function testing.

INTRODUCTION

The prevalence and incidence of asthma has increased over the recent decades [1, 2]. Besides an improved awareness of the disease, there are several other explanations for the increased asthma prevalence, such as air pollution, exposure to tobacco smoke, change in diet and obesity [2]. Recently, the incidence and prevalence of obesity have increased concurrently with the incidence and prevalence of asthma, suggesting a possible link between obesity and asthma [3, 4].

International guidelines advise that asthma diagnosis should be based on both the presence of symptoms and objective measurements of variable airflow obstruction or bronchial hyperresponsiveness (BHR) [1]. However, in daily practice spirometry or provocation tests are not always performed, and the diagnosis of asthma is mainly based on symptoms [5]. Since obese patients report more dyspnea and asthma-like symptoms than non-obese patients [6, 7], it might be that they unjustified get labelled as asthma (overdiagnosis) without performing adequate diagnostics. Inevitably, any misdiagnosis may lead to inappropriate treatment [5], with increased risk of side-effects and increased costs [8].

Many epidemiological studies concerning obesity and asthma have used physician-diagnosed asthma without confirmation by pulmonary function tests. This implies reasonable doubt as to the correctness of the diagnosis. Multiple studies report that asthma could be excluded after extensive testing in 30% of physician-diagnosed asthma [9-11], even after stopping with asthma medication [12]. On the other hand, missing the diagnosis of asthma in this population is also an important issue. Impaired dyspnea perception is especially thought to play a role in severe asthma [13, 14], and poor perception of airflow obstruction may lead to under- treatment of asthma [15, 16]. All the recent studies concerning overdiagnosis of asthma in the obese [11, 12, 17], initially used selected subjects with asthma, and therefore did not take into account obese patients in which asthma was not detected. Therefore, the information about underdiagnosis of asthma in the obese is incomplete.

The hypothesis of the present study was that underdiagnosis of asthma is also present in the morbidly obese. We therefore used an extensive diagnostic algorithm to investigate whether in addition to overdiagnosis also underdiagnosis of asthma is present in a morbidly obese cohort, which was recruited from a pre-operative screening program for bariatric surgery.

METHODS

Study population

The subjects included in this study were patients who underwent pre-operative screening before bariatric surgery in the Sint Franciscus Gasthuis in Rotterdam, the Netherlands from September 2009 to April 2011. Eligibility criteria for bariatric surgery were: age between 18 and 60 years old, body mass index (BMI) ≥ 35 kg/m^2. We excluded people who (a) were older than 50 years of age or; (b) had a history of smoking more than 10 cigarettes a day, or were currently smoking more than 10 cigarettes a day (with the aim to decrease the risk of including subjects with chronic obstructive pulmonary disease [COPD]); (c) were taking oral corticosteroid therapy; (d) had an asthma exacerbation four weeks before screening; (e) were unable to perform pulmonary function tests; or (f) had pulmonary disease other than asthma.

We aimed for 40 subjects with, and 40 subjects without asthma, as this study is a part of a longitudinal study. All subjects underwent baseline physical examinations including routine assessment of anthropometry, blood pressure and blood samples. Waist circumference was measured directly to the body surface midway between the lower rib margin and the ileac crest. Fat free mass and fat weight (in kg and % body weight) were measured using bio-electrical impedance analysis (Bodystat 1500, Bodystat Ltd, British Isles) [18].

All subjects gave written informed consent and the local ethics committee (Toetsingscommissie Wetenschappenlijk Onderzoek Rotterdam e.o.) approved the study protocol (Netherlands Trial Register 3204).

Pulmonary function tests

All subjects underwent lung function testing for the presence of reversible airflow obstruction as part of the screening protocol before bariatric surgery. Spirometry was performed with Vmax spirometer (Vmax SensorMedics Viasys, type Encore 20/22/229/62 Encore, Cardinal Health, USA) before and after 400 μg of inhaled salbutamol, according to the American Thoracic Society / European Respiratory Society guidelines [19]. All values obtained were related to height, age and gender and expressed as percentage of their predicted value (reference ERS 1993[20]). The pulmonary function results are prebronchodilator values unless otherwise specified.

All subjects who met the inclusion criteria were invited for a second visit for further lung function evaluation. Again, if applicable, subjects were asked not to use long-acting β-agonists for 48 hours, short-acting β-agonists for 8 hours and antihistamines or antileukotriene medication 72 hours before lung function testing. Subjects who were using inhaled corticosteroids (ICS), were asked to voluntarily discontinue this. Daily symptom diary and daily peak flow rates were used to optimally screen asthma control.

Subjects were permitted to use short-acting bronchodilators as rescue medication. After six weeks they returned for their second visit, during which exhaled Nitric Oxide (Fe_{NO})(Niox mino Aerocrine, Sweden) [21], impulse oscillometry (IOS) (Masterscreen IOS system, Erich Jaeger Co., Würzburg, Germany), diffusion capacity (intrabreath method, corrected for hemoglobin and alveolar volume) [22] and methacholine provocation testing (five breath dosimeter method) [23, 24] were performed. Bronchial responsiveness to methacholine was expressed as the provocative dose of methacholine inducing a 20% fall in FEV_1 (PD_{20}). A PD_{20} < 1.8 mg was considered as a positive provocation test. If the methacholine provocation test was negative, a second provocation test was performed six weeks later. Subjects who refused to stop the ICS, or subjects who had exacerbations of asthma symptoms during the 12 weeks of discontinuing their medication, underwent provocation testing while using ICS (figure 2a, supplementary files).

Definition of asthma

Asthma was defined according to GINA guidelines [1] as both the presence of symptoms and either an increase of ≥12% and 200 ml in FEV_1 after salbutamol, or a positive provocation test. Physician diagnosis of asthma was scored as a positive reaction to the following question "Did a medical doctor ever told you that you have asthma?". Patients with a physician diagnosis of asthma and fulfilling the criteria of asthma were defined as having a correct asthma diagnosis. Those without physician diagnosed asthma, but who fulfilled the criteria for asthma were defined as underdiagnosed. The subjects with physician-diagnosed asthma, but who not fulfilled the criteria of asthma after stopping inhaled corticosteroids for more than 6 weeks were defined as overdiagnosed. Patients without airway reversibility and a negative provocation test formed the control group (figure 2b, supplementary files).

Questionnaires

Asthma symptoms were assessed by the mini Asthma Quality of Life Questionnaire (AQLQ) [25] and the Asthma Control Questionnaire (ACQ) [26] to assess asthma complaints. The Epworth Sleepiness Scale [27] questionnaire was used to assess OSAS, and the GERD-Questionnaire for gastro-esophageal reflux disease (GERD) [28]. The average of 7 days with an activity meter was used to determine the total number of steps taken a day, as a measure of activity.

Atopy

Atopic status was assessed with skin-prick tests (SPT) with a battery of common aeroallergens: house-dust mite; dog, cat, and horse dander; *Aspergillus fumigatus*; mugwort; and birch and grass pollen (Vivodiagnost; ALK Benelux BV, Groningen, The Netherlands). SPT cutaneous response was compared with a histamine-positive control and a saline

solution–negative control. A positive result was defined as at least one response with a wheal diameter ≥ 3 mm after 15 minutes. Total IgE and specific plasma IgE were determined with a solid-phase two-step chemiluminescent immunoassay on the Immulite 2000 (Siemens, Los Angeles, CA). A positive inhalation screen was defined as at least one increased amount of specific IgE for fungus, house-dust mite, cat, dog, grass, birch or herbs.

Laboratory

Blood cell counts and 5-part leukocyte differentiation were determined automatically using LH750 analyzers (Beckman Coulter Miami, FL, USA). CRP was measured using LX 20 and DxC analyzers (Beckman Coulter, Miami, FL, USA). Vitamin D was determined by RIA or chemiluminescence (LIA) on Liason analyzers (DiaSorin, Stillwater, MN, USA).

Statistical analyses

Underdiagnosis of asthma subjects were consecutively compared with correctly diagnosed asthma, overdiagnosis of asthma and controls. Unless indicated otherwise, all data are expressed as median (min-max) for scale variables or percentage for categorical variables. Unadjusted between groups comparisons were performed using Mann Withney U test, Chi square or Fisher exact test as appropriate. Cohen's Kappa coefficient was calculated as a measure of inter-rater agreement. IgE and Fe_{NO} were log transformed for statistical purposes. All analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, Illinois, USA). Results were evaluated at 95% confidence interval at a two-sided significance threshold of $p<0.005$ (Bonferroni correction for multiple testing).

RESULTS

Demographics

In total 473 patients were screened. 220 subjects met the inclusion criteria, and 86 subjects agreed to participate in the study. The most frequently reported reasons for refusing participation were "no time for additional appointments due to work" and "distance to hospital too far". The 136 subjects who declined consent did not significantly differ in demographic characteristics from the participants (BMI, weight, abdominal circumference, age or gender; data not shown) (figure 1).

From the 86 assessed patients, 32 patients had physician-diagnosed asthma. However, using the diagnostic algorithm, asthma could be excluded based on the absence of reversibility in FEV_1 or negative provocation test in 13 of these subjects (41%, 95%CI [0.24-0.50]) (overdiagnosis). In contrast, when analyzing the 54 patients without physician-diagnosed asthma, we found that 17 patients (31%, 95%CI [0.20-0.46]) had

symptoms and a reversible airflow obstruction or airway hyperreactivity (underdiagnosis). This way, among the 86 assessed subjects, 36 true asthma patients were diagnosed and 50 true controls. Cohen's Kappa coefficient between physician diagnosed asthma and our diagnosis of asthma was 0.251. Table 1 shows the baseline characteristics of the four groups. There were no significant differences in demographic characteristics between the groups, especially not in age, body mass index or weight. However, the

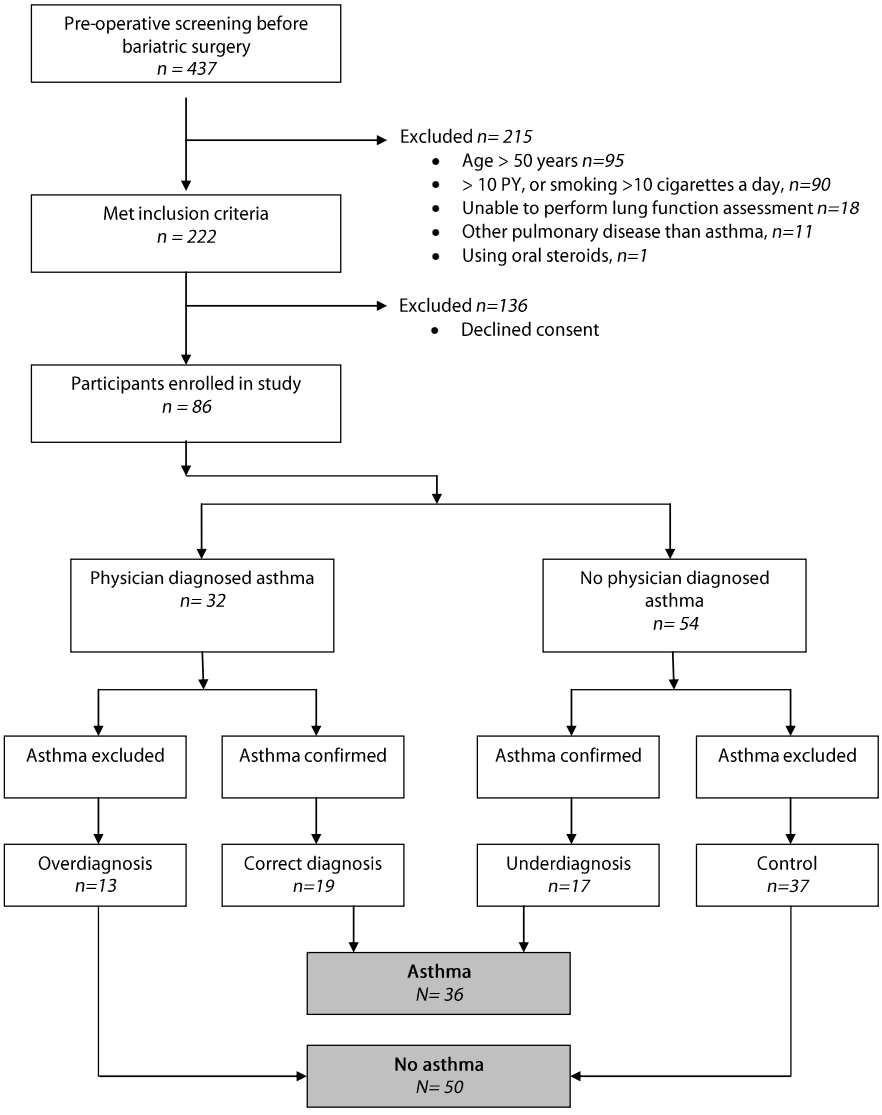

Figure 1 Selection of participants and study outcome

subjects with underdiagnosis of asthma had a significantly larger abdominal circumference than the controls.

Symptoms and questionnaires

There were no differences in symptoms between the group with an underdiagnosis of asthma and the correctly diagnosed asthma group or the overdiagnosis asthma group (table 2). The underdiagnosis group trended toward having more complaints of wheezing and coughing than the control group. There was also a trend that the asthma control questionnaire (ACQ) was better for the underdiagnosis group compared to the correctly diagnosed asthma group. The ACQ of the underdiagnosis group was comparable with the overdiagnosis group, and significantly better than the controls. The asthma quality of life questionnaire (AQLQ) was significant worse for the underdiagnosis group, compared with the controls, and comparable with the correctly diagnosis asthma and overdiagnosis asthma groups.

Medication use

Eleven of the patients with correctly diagnosed asthma were using ICS at the start of the study. Three refused to stop the ICS. Of the eight subjects who withheld their ICS, two had an increase of asthma symptoms and resumed their ICS. Also, three asthmatics without ICS before the start of the study had an increase in asthma symptoms, and started with ICS. In the overdiagnosed subjects, three were using ICS at the start of the study, and all agreed to withhold their ICS, without any change in symptoms.

Lung function parameters

A methacholine provocation test was not performed in two of the underdiagnosed subjects, because of low FEV_1 (n=1) and extreme obesity (BMI 71, n=1), and once in the correct diagnosis asthma group because of poor lung function technique. All three, however, had reversible airway obstruction (delta $FEV_1 \geq 12\%$). 18 correctly diagnosed asthmatics had a positive provocation test, of which 8 also had reversible airway obstruction. 11 of the underdiagnosed subjects had a positive provocation test, of which only one also had reversible airway obstruction. The diagnosis asthma was only based on reversibility, with a negative provocation test in 4 underdiagnosed asthmatics.

There was no difference in lung volumes, Fe_{NO} or diffusion capacity between the investigated groups. Among the parameters of the IOS there was a trend that R_5 and F_{res} were higher in the underdiagnosed group compared to the control group (table 3).

Blood parameters

With regard to the laboratory parameters (table 3), there was no difference between the investigated groups.

Table 1 Demographics of study population

	Underdiagnosis asthma N=17	Correct asthma diagnosis N=19	Overdiagnosis asthma N= 13	Control N=37	p Value [1]	p Value [2]	p Value [3]
Gender (%female)	77%	79%	92%	78%	1.000	0.355	1.000
Ethnicity (%non-Caucasian)	24%	11%	8%	14%	0.391	0.355	0.439
Age (years)	36 (19-49)	33 (24-48)	39 (19-50)	37 (18-50)	0.590	0.543	0.479
Weight (kg)	131 (111-240)	131 (101-191)	126 (99-157)	123 (94-199)	0.568	0.391	0.144
Body Mass index (kg/m^2)	45.8 (38.7-74.8)	45.1 (38.4-63.8)	45.4 (37.4-53.8)	42.3 (35.6-60.0)	0.788	0.660	0.171
Abdominal circumference (cm)	137 (118-165)	129 (112-158)	130 (109-142)	125 (98-200)	0.206	0.013	0.005
Bio-impedance							
Fat free Mass	65.7 (47.8-100.5)	60.9 (50.3-94.8)	61.4 (50.9-72.6)	62.5 (47.2-83.9)	0.448	0.464	0.385
Fat weight (%)	50.9 (40.7-64.1)	52.8 (37.6-70.4)	51.6 (46.5-58.6)	50.2 (31.1-59.7)	0.499	0.568	0.578
Fat weight (kg)	68.5 (55.7-141.0)	69.1 (44.5-134.4)	64.0 (52.8-83.8)	59.2 (32.0-100.0)	0.934	0.754	0.057
Smoking status							
% never smoked	59%	53%	54%	78%	0.865	0.932	0.236
% stopped smoking	18%	16%	23%	14%			
% current smoker	23%	31%	23%	8%			
Pack years	0 (0-9)	0 (0-10)	0 (0-10)	0 (0-9)	0.589	0.764	0.119

Data are presented as median (min-max)

[1] p value for comparison between underdiagnosis asthma and correct asthma diagnosis

[2] p value for comparison between underdiagnosis asthma and overdiagnosis asthma

[3] p value for comparison between underdiagnosis asthma and control

Table 2 Symptoms, questionnaires, and medication use

	Underdiagnosis asthma N=17	Correct asthma diagnosis N=19	Overdiagnosis asthma N= 13	Control N=37	p Value [1]	p Value [2]	p Value[3]
Symptoms previous 12 months							
Dyspnea at rest	17.6%	47.4%	15.4%	5.4%	0.083	1.000	0.311
Dyspnea on exertion	94.1%	89.5%	84.6%	81.1%	1.000	0.565	0.411
Dyspnea at night	11.8%	42.1%	30.8%	5.4%	0.065	0.360	0.582
Wheezing	47.1%	84.2%	76.9%	18.9%	0.033	0.141	0.032
Coughing	52.9%	73.7%	76.9%	18.9%	0.299	0.259	0.011
Asthma Control Questionnaire[4]	0.9 (0.4-1.9)	1.4 (0.3-2.9)	0.8 (0-2.9)	0.3 (0-2.3)	0.021	0.563	<0.001
Asthma Quality of Life Questionnaire (total) [5]							
AQLQ symptoms	6.1 (5.2-6.8)	5.3 (3.7-7.0)	5.5 (3.7-6.6)	6.7 (4.9-7.0)	0.016	0.069	0.002
AQLQ activities	5.8 (4.6-6.6)	4.6 (3.6-7.0)	5.5 (3.4-6.8)	6.6 (3.8-7.0)	0.045	0.202	<0.001
AQLQ emotions	5.8 (3.5-6.8)	5.3 (1.8-7.0)	5.4 (3.0-7.0)	7.0 (3.3-7.0)	0.641	0.505	0.001
AQLQ environment	7.0 (5.7-7.0)	6.3 (4.3-7.0)	6.7 (5.0-7.0)	7.0 (6.3-7.0)	0.018	0.172	0.018
	6.7 (4.0-7.0)	4.7 (2.0-7.0)	4.5 (3.0-7.0)	6.7 (3.0-7.0)	0.002	0.006	0.444
Medication use at inclusion study							
Short acting bronchodilator	0%	74%	77%	0%	<0.001	<0.001	1.000
Long acting bronchodilator	0%	11%	8%	0%	0487	0.433	1.000
Antileukotrienes	0%	0%	8%	0%	1.000	0.433	1.000
B_2 sympaticomimetica/ ICS	0%	32%	23%	0%	0.020	0.070	1.000
Inhaled corticosteroids	0%	32%	23%	0%	0.020	0.070	1.000
Antihistamines	12%	32%	15%	11%	0.236	1.000	1.000
Nasal corticosteroids	0%	26%	15%	8%	0.047	0.179	0.544

Data are presented as median (min-max)
[1] p value for comparison between underdiagnosis asthma and correct asthma diagnosis
[2] p value for comparison between underdiagnosis asthma and overdiagnosis asthma
[3] p value for comparison between underdiagnosis asthma and control
[4] scores of the Asthma Control Questionnaire range from 0 to 6, with lower scores indicating better asthma control
[5] scores of the Asthma Quality of Life Questionnaire range from 1 to 7, with higher scores indicating better asthma-specific quality of life
ICS, inhaled corticosteroid.

Allergy, activity and comorbidity

There was no difference in allergy, reflected in either a positive inhalation screen or a positive SPT, or rhinitis between the investigated groups (table 3).

To assess the activity of the subjects, a step-counter was used, which showed no significant differences between the investigated groups. There were also no differences in comorbidities, such as obstructive sleep apnea syndrome (Epworth Sleepiness Scale) or reflux (GERD-questionnaire) (both table 3), or the presence of the metabolic syndrome.

DISCUSSION

We found that after discontinuation of inhaled corticosteroids and extensive lung function and provocation tests, misdiagnosis of asthma was present in our morbidly obese cohort. In addition to confirming previous reports on overdiagnosis of asthma, importantly we also found that a substantial proportion of morbidly obese asthma patients were underdiagnosed. This indicates that in the morbidly obese, the diagnosis of asthma cannot be made on asthma-like symptoms alone, and lung function testing is an essential part of the diagnosis of asthma, as confirmed with a low Cohen's kappa coefficient for physicians and our diagnosis of asthma.

This is, to our knowledge, the first study investigating both overdiagnosis and underdiagnosis of asthma in an obese cohort. Furthermore, we have used an extensive diagnostic algorithm to confirm or exclude asthma. In addition, we have also looked at co-morbidities such as reflux and OSAS, which are abundant in the obese and are known to influence asthma. Moreover, also cofactors such as immobility and allergy were taken into account.

We confirm previous reports showing that overdiagnosis of asthma is present in the morbidly obese [11, 12, 17], although Aaron found that overdiagnosis of asthma was overall no more likely to occur among obese individuals than among non-obese individuals. However, in studies so far concerning overdiagnosis of asthma, assessment of underdiagnosis was not part of these studies. We also found underdiagnosis of asthma in our cohort of morbidly obese subjects, a previously overlooked problem.

In the present study symptoms turned out to be unreliable for an adequate diagnosis of asthma. Subjects with an overdiagnosis of asthma reported asthma-like symptoms, which explain the overdiagnosis. Interestingly, patients who were underdiagnosed for asthma also had symptoms. The reason why they did not receive a previous diagnosis of asthma is not clear, but may be explained by two factors. First, this discrepancy might be due to self-misperception; the patients themselves did not relate their symptoms to respiratory disease but rather to obesity and did not contact a physician for these complaints. A second possibility could be that they did contact a physician for dyspnea,

Table 3 Pulmonary function, laboratory and co morbidity

	Underdiagnosis asthma N=17	**Correct asthma diagnosis N=19**	**Overdiagnosis asthma N= 13**	**Control N=37**	**p Value [1]**	**p Value[2]**	**p Value [3]**
Spirometry							
FEV_1, pre(% predicted)	85 (62-99)	88 (66-119)	99 (84-125)	96 (73-120)	0.260	<0.001	0.001
FEV_1, post (% predicted)	92 (72-118)	96 (74-118)	102 (90-129)	99 (75-124)	0.738	0.025	0.002
FVC, pre (% predicted)	93 (74-112)	100 (75-128)	108 (91-133)	102 (77-144)	0.154	0.004	0.019
FEV1/FVC, pre (% predicted)	77 (63-92)	75 (66-86)	81 (74-87)	82 (66-93)	0.465	0.039	0.010
RV, post (% predicted) *	71 (39-117)	69 (39-126)	76 (48-118)	72 (33-96)	0.595	0.596	0.764
TLC, post (% predicted) *	94 (83-100)	100 (80-106)	97 (85-114)	94 (75-114)	0.104	0.180	0.920
FRC, post (% predicted) *	61 (40-87)	56 (47-95)	64 (51-88)	63 (41-85)	0.682	0.910	0.737
RV/TLC, post (% predicted) *	19 (12-35)	24 (10-41)	24 (14-41)	25 (12-86)	0.289	0.176	0.146
FEF_{25-75}, pre (% predicted)	75 (33-119)	69 (38-111)	97 (64-118)	96 (49-135)	0.751	0.009	0.003
Reversibility FEV_1	10 (-6-20)	9 (-1-20)	4 (-7-9)	4 (-2-11)	1.000	0.009	0.001
Fe_{NO} (bbp) **	16 (5-89)	14 (8-45)	11 (3-18)	16 (5-47)	0.968	0.087	0.783
Diffusion capacity (% predicted)	97 (83-133)	95 (69-130)	97 (69-134)	95 (75-132)	0.333	0.769	0.132
IOS							
R_5 (kPa/sec)	0.69 (0.44-1.06)	0.76 (0.42-1.39)	0.59 (0.44-0.85)	0.56 (0.17-0.97)	0.738	0.139	0.008
R_{20} (kPa/sec)	0.45 (0.30-0.76)	0.40 (0.27-1.03)	0.71 (0.26-0.68)	0.42 (0.18-0.67)	0.317	0.139	0.143
X_5 (kPa/sec)	-0.24 (-0.42- -0.16)	-0.29 (-0.87- -0.11)	-0.24 (-0.40- -0.16)	-0.19 (-0.43- -0.08)	0.615	0.999	0.049
F_{res} (Hz)	22.0 (16.0-24.9)	22.8 (10.5-30.3)	18.7 (14.0-23.2)	16.3 (8.4-28.7)	0.738	0.139	0.008
Peripheral blood count							
Leukocytes (10^9 /L)	8.5 (5-12)	8.9 (6-13)	7.1 (6-12)	7.4 (5-11)	0.477	0.288	0.084
Neutrophils (%)	65 (50-72)	61 (45-72)	59 (47-70)	59 (46-69)	0.555	0.166	0.099
Lymphocytes (%)	27 (15-38)	28 (17-45)	33 (20-43)	31 (23-47)	0.835	0.112	0.095
Monocytes (%)	6.61 (4.66-8.50)	6.74 (5.55-12.76)	6.45 (4.00-9.00)	6.41 (4.00-13.43)	0.795	0.945	0.840

3 Pulmonary function, laboratory and co morbidity (continued)

	Underdiagnosis asthma N=17	Correct asthma diagnosis N=19	Overdiagnosis asthma N= 13	Control N=37	p Value [1]	p Value [2]	p Value [3]
Eosinophils (%)	2.49 (0.54-9.09)	2.35 (0.47-8.00)	2.00 (1.00-4.00)	2.04 (0.40-7.85)	0.887	0.835	0.437
Basophils (%)	0.38 (0.00-1.00)	0.52 (0.00-1.19)	0.13 (0.00-1.51)	0.50 (0.00-2.45)	0.339	0.560	0.202
IgE (kU/L) **	105 (7-3419)	202 (11-1838)	66.4 (10-273)	71.6 (1.5-587)	0.520	0.072	0.430
CRP (mg/L)	7 (1-28)	8 (3-25)	7 (5-21)	9 (1-24)	1.000	0.724	0.858
Vitamin D (nmol/L)	27 (11-78)	37 (12-89)	39 (18-62)	41 (10-83)	0.438	0.232	0.205
Rhinitis	41%	84%	62%	30%	0.014	0.462	0.407
Positive inhalation screen	63%	73%	39%	38%	0.478	0.272	0.098
Skin prick test (% ≥1 positive wheal)	47%	74%	36%	32%	0.160	0.701	0.334
Epworth Sleepiness Scale	2 (0-7)	3 (0-8)	2 (0-9)	2 (0-15)	0.351	0.770	0.786
GERD-questionnaire	6 (4-10)	7 (4-12)	6 (2-10)	6.5 (3-14)	0.074	0.146	0.022
Metabolic syndrome	53%	61%	75%	40%	0.738	0.273	0.335
Steps a day	4360 (1309-10840)	5642 (2156-12176)	6197 (4456-10083)	4730 (2061-11705)	0.415	0.096	0.829

Data are presented as median (min-max)

* Because of weight limitations (<150 kg) of bodybox different numbers; underdiagnosis asthma n=11, correct asthma diagnosis n=10, overdiagnosis asthma n= 10, control n=26

** log transformed for statistical purposes

[1] p value for comparison between underdiagnosis asthma and correct asthma diagnosis

[2] p value for comparison between underdiagnosis asthma and overdiagnosis asthma

[3] p value for comparison between underdiagnosis asthma and control

Diffision capacity, kCO; ERV, expiratory reserve volume; FEF_{25-75} , Forced expiratory flow at 25% point to the 75% point of Forced Vital Capacity; FEV_1, forced expiratory volume in 1 second; Fe_{NO}, exhaled nitric oxide; FRC, functional residual capacity; FVC, forced vital capacity; RV,residual volume; TLC, total lung capacity.

but these discomforts were attributed to obesity by the physician (physician misperception). Self-misperception of respiratory symptoms is probably the most relevant factor [29], and might be partly explained by worse perception of dyspnea. Unfortunately, no data were available on previous visits to a physician because of respiratory symptoms.

Interestingly, especially R_5 – a marker of both central and distal airways obstruction – was particularly high in the underdiagnosed subjects. The underdiagnosed subjects, in particular, had a large abdominal circumference in our study. Therefore, central obesity may lead to obstruction of the peripheral airways, which may be more related to poor perception of dyspnea than proximal airway obstruction. This suggests that it is not the amount of fat, but the location of the fat, which influences asthma perceptions, which is also supported by a study from Lessard [30]. Similar to the symptoms, the inappropriate use of inhaled medication was high in the overdiagnosis asthma group. This may result in serious side effects and, moreover, contributes to the economic burden of asthma. The symptoms could not be explained by a restriction or a low diffusion capacity. There was no difference in smoking status, furthermore as result of the exclusion criteria, the median number of pack years was nihil, so smoking is unlikely to be a contribution factor. There was no difference in co-morbidities such as allergy, GERD, OSAS or activity between asthmatics and controls, and therefore these factors do not seem to play a role in asthma in the obese.

There were few differences between the underdiagnosed and the overdiagnosed subjects. However, many of the overdiagnosed subjects had rhinitis, which can cause dyspnea perception[31]. Furthermore, the overdiagnosed scored low for the AQLQ, especially in the environment domain, a domain where symptoms related to external stimuli are scored. However, by definition, all overdiagnosed had a negative provocation test. This reduced QOL in morbidly obese overdiagnosed asthma subjects was also found by Scott *et al.* [11]. These data suggest that the discrepancy between pulmonary function test and the AQLQ, might in part be explained by rhinitis.

There are several limitations to our study. Only 39% of potentially eligible subjects agreed to participate. So a volunteer bias could have influenced the study results. The large proportion of declines is most probably due to the fact that this study is a part of a longitudinal study. Another effect of this study being a part of another study, is the fact that we aimed for 40 subjects with and 40 subjects without asthma and that inclusion of the latter group went faster, so subjects were not enrolled in a consecutive order. So the prevalence of physician diagnosed asthma in our study cohort is biased, and therefore also the prevalence of under- or overdiagnosis of asthma is biased. Importantly, however, there were no differences in patient demographics between the subjects who declined consent and those who participated. Since a lean control group was not part of the study, it is not clear whether underdiagnosis is more prevalent among the obese compared to a lean cohort. The selection of subjects willing to undergo bariatric surgery

could also have led to a selection bias. And finally, the small group of misdiagnosed subjects (either over- or underdiagnosis) could have given us power problems to find differences in subgroup analysis.

In summary, both overdiagnosis as well as underdiagnosis of asthma occurs in the morbidly obese. A diagnosis of asthma based on symptoms alone is unreliable in the morbidly obese, and pulmonary function testing is an essential part of the diagnosis of asthma in the morbidly obese. As a result of the most likely high prevalence, potential health risk and the high economic burden of misdiagnosis, characterization of these patients is important. Further research aiming at the effects of weight reduction on quality of life and symptoms, not only in asthmatics but also in the overdiagnosed can provide valuable further insights into this interesting problem.

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REFERENCES

1. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31(1):143-78.
2. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355(21):2226-35.
3. Chinn S. Asthma and obesity: where are we now? *Thorax* 2003;58(12):1008-10.
4. Camargo CA, Jr., Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;159(21):2582-8.
5. Lucas AE, Smeenk FW, Smeele IJ, van Schayck CP. Overtreatment with inhaled corticosteroids and diagnostic problems in primary care patients, an exploratory study. *Fam Pract* 2008;25(2):86-91.
6. Pakhale S, Doucette S, Vandemheen K, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Aaron SD. A comparison of obese and nonobese asthmatics: Exploring an asthma-obesity interaction. *Chest* 2010;137:1316-1323.
7. Babb TG, Ranasinghe KG, Comeau LA, Semon TL, Schwartz B. Dyspnea on exertion in obese women: association with an increased oxygen cost of breathing. *Am J Respir Crit Care Med* 2008; 178(2):116-23.
8. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, FitzGerald JM. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
9. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct? *Fam Pract* 1999;16(2):112-6.
10. LindenSmith J, Morrison D, Deveau C, Hernandez P. Overdiagnosis of asthma in the community. *Can Respir J* 2004;11(2):111-6.
11. Scott S, Currie J, Albert P, Calverley P, Wilding JP. Risk of mis-diagnosis, Health related Quality of Life and Body Mass Index in Overweight Patients with doctor diagnosed asthma. *Chest* 2012; 141(3):616-24.
12. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Doucette S, Fergusson D. Overdiagnosis of asthma in obese and nonobese adults. *Cmaj* 2008;179(11):1121-31.
13. Veen JC, Smits HH, Ravensberg AJ, Hiemstra PS, Sterk PJ, Bel EH. Impaired perception of dyspnea in patients with severe asthma. Relation to sputum eosinophils. *Am J Respir Crit Care Med* 1998; 158(4):1134-41.
14. Bijl-Hofland ID, Cloosterman SG, Folgering HT, Akkermans RP, van Schayck CP. Relation of the perception of airway obstruction to the severity of asthma. *Thorax* 1999;54(1):15-19.
15. Boulet LP, Leblanc P, Turcotte H. Perception scoring of induced bronchoconstriction as an index of awareness of asthma symptoms. *Chest* 1994;105(5):1430-3.
16. van den Toorn LM, Overbeek SE, Prins JB, Hoogsteden HC, De Jongste JC. Dyspnoea perception during clinical remission of atopic asthma. *Eur Respir J* 2002;19(6):1047-50.
17. Luks VP, Vandemheen KL, Aaron SD. Confirmation of asthma in an era of overdiagnosis. *Eur Respir J* 2010;36(2):255-60.
18. Fuller NJ, Sawyer MB, Elia M. Comparative evaluation of body composition methods and predictions, and calculation of density and hydration fraction of fat-free mass, in obese women. *Int J Obes Relat Metab Disord* 1994;18(7):503-12.
19. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005;26(2):319-38.

20. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5-40.
21. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171(8):912-30.
22. Huang YC, O'Brien SR, MacIntyre NR. Intrabreath diffusing capacity of the lung in healthy individuals at rest and during exercise. *Chest* 2002;122(1):177-85.
23. Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O'Byrne PM, Anderson SD, Juniper EF, Malo JL. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:53-83.
24. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, Cockcroft DW, Fish JE, Sterk PJ. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;161(1):309-29.
25. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14(1):32-8.
26. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14(4):902-7.
27. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540-5.
28. Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, Lind T. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 2009;30(10):1030-8.
29. van Schayck CP, van Der Heijden FM, van Den Boom G, Tirimanna PR, van Herwaarden CL. Underdiagnosis of asthma: is the doctor or the patient to blame? The DIMCA project. *Thorax* 2000;55(7): 562-5.
30. Lessard A, Almeras N, Turcotte H, Tremblay A, Despres JP, Boulet LP. Adiposity and pulmonary function: relationship with body fat distribution and systemic inflammation. *Clin Invest Med* 2010; 34(2):E64-70.
31. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;161(6):2051-7.

SUPPLEMENTARY DATA

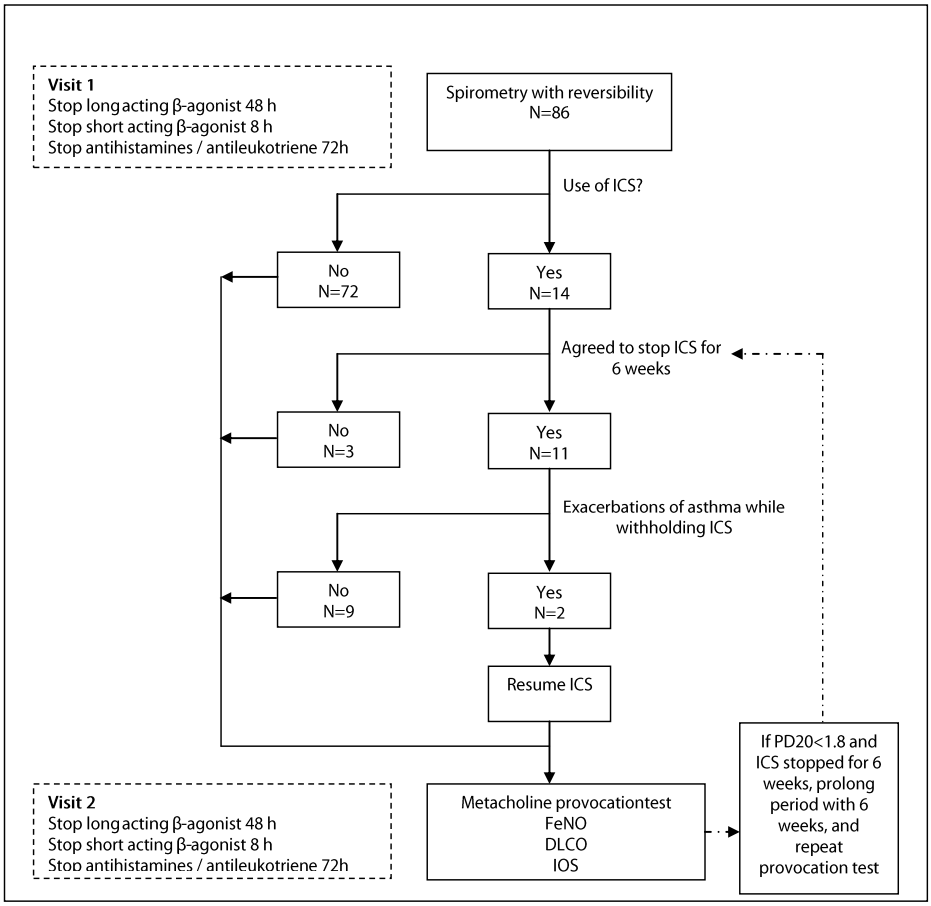

Figure 2a Diagnostic algorithm

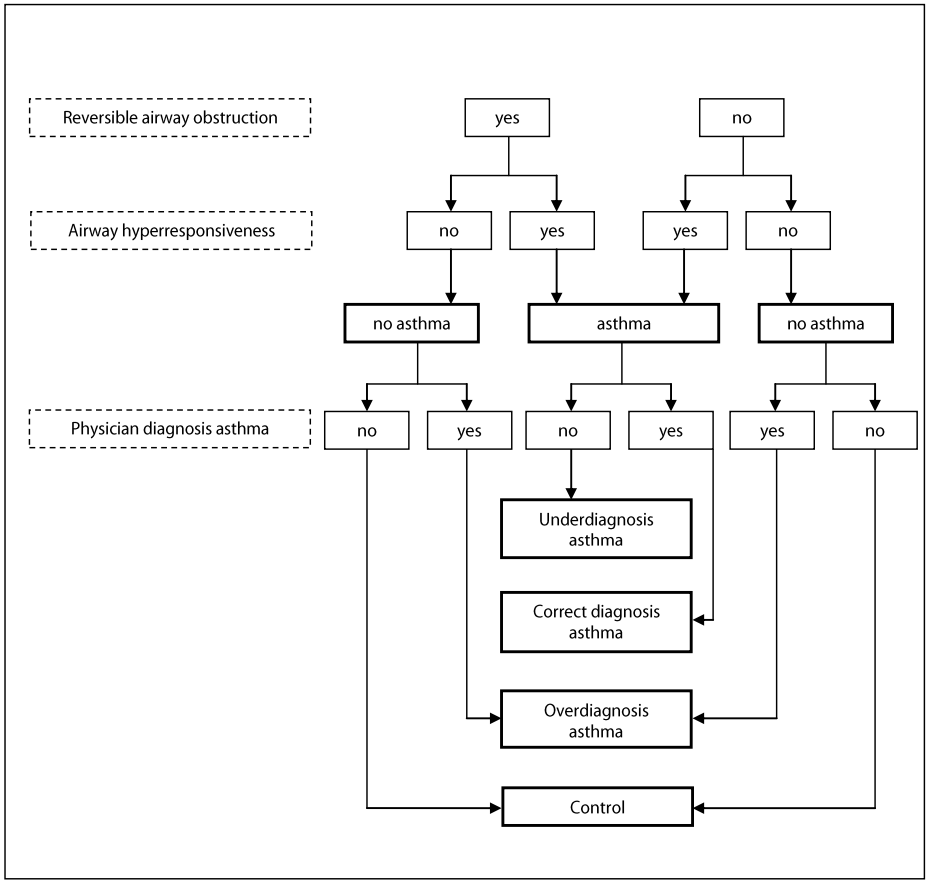

Figure 2b Diagnostic algorithm

PART B

BRONCHIAL AND SYSTEMIC INFLAMMATION IN THE MORBIDLY OBESE

3

Obesity and asthma: co-morbidity or causal relationship?

Van Huisstede A, Braunstahl GJ.

Monaldi Archives Chest Disease, 2010;73(3):116-23

ABSTRACT

There is substantial evidence that obesity and asthma are related. "Obese asthma" may be a unique phenotype of asthma, characterized by decreased lung volumes, greater symptoms for a given degree of lung function impairment, destabilization or lack of asthma control, lack of eosinophilic inflammation and a different response to controller medication.

Whether this relationship between obesity and asthma is causal or represents co-morbidity due to other factors is unclear. In previous reviews concerning the relationship between obesity and asthma, five hypotheses were put forth. One of these hypotheses is that a low grade systemic inflammation caused by adipokines from the fat tissue causes or enhances bronchial inflammation. In animal models, there is an increasing amount of evidence for the role of adipokines derived from fat tissue in the relationship between obesity and asthma. The data are conflicting in humans.

Since obesity is a component of the metabolic syndrome and the metabolic syndrome is also a form of systemic inflammation, it is to be expected that there is a relationship between metabolic syndrome and asthma. The few data that are available show that there is no relationship between metabolic syndrome and asthma, but there is one between the metabolic syndrome and asthma-like symptoms.

Further research is needed to confirm the relationship between obesity and asthma in humans, where a rigorous approach in the diagnosis of asthma is essential.

INTRODUCTION

Obesity is currently a major health problem and is developing into a global epidemic. Obesity is classified by the Body Mass Index (BMI) (table 1) and is defined as abnormal or excessive fat accumulation which can cause health problems. The World Health Organisation's (WHO) latest projections indicate that, globally in 2005, approximately 1.6 billion adults (age 15+) were overweight, and at least 400 million adults were obese. WHO further predicts that, by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese[1].

Because the prevalence of both obesity and asthma have increased in the recent years, many studies have examined the possibility of a causal relationship between these two conditions[2-5]. The fact that asthma improves after weight loss with either bariatric surgery or low caloric diet supports the relationship between obesity and asthma[6]. Moreover, obese patients with persistent asthma have significantly worse asthma-related quality of life[7], less asthma control[8, 9], more severe disease[4, 10-12], and more asthma-related hospital admissions than asthma patients with a normal BMI.

There are multiple hypotheses that may explain the relationship between obesity and asthma. This review will discuss the different hypotheses, and will focus on the systemic inflammation, and the possible role of the metabolic syndrome.

Table 1 BMI classification

BMI (kg/m^2)	Classification
<18.5	Underweight
18.5-25	Normal weight
25-30	Overweight
30-40	Obesity
>40	Morbid Obesity

Classification of different BMI-classes. BMI, Body Mass Index

Asthma phenotype in obesity

Recent data suggest[13, 14] that obese patients have a different phenotype of asthma, characterized by female predominance, late onset of asthma and high symptom expression.

Classical asthma is characterised by a Th-2 cell mediated allergic airway inflammation. The characteristics of airway inflammation in asthma (exhaled nitric oxide (eNO) and inflammatory cells in induced sputum) have been investigated in obesity. eNO can be seen as a marker of eosinophilic inflammation in the airways. De Winter *et al.* showed that a higher BMI was associated with a higher eNO in healthy patients[15]. On the con-

trary, Kazaks found no significant relationship between exhaled NO and BMI in adult asthma patients[16]. However, there was no correction for use of corticosteroids.

Sputum eosinophilia is a hallmark of asthma. Several studies have found no - or even an inverse - relationship between the number of sputum eosinophils and BMI[17-19]. Although airway eosinophil accumulation is characteristic for asthma, little is known about the influence of obesity on eosinophil migration from bone marrow to the bronchial mucosa. Calixto[20] found, in a murine model of asthma, that diet-induced obesity enhanced eosinophil trafficking from bone marrow to the airway, but delayed their transit through the airway epithelium into the airway lumen.

If the relationship between asthma and obesity could be explained by allergic airway inflammation, then one would expect a relationship between obesity and other allergic conditions, such as allergic rhinitis or allergic conjunctivitis. Although several epidemiologic studies have reported an increased risk of atopy in the overweight and/or obese[21, 22], others have demonstrated an increased risk of developing asthma in non-allergic compared to allergic adults[23-25].

In summary, there is a great deal of conflicting data concerning the signs of bronchial inflammation in obese asthmatics (eNO, sputum eosinphilia). Data suggest that asthma in obese patients is not characterized by a classic Th2 cell driven inflammation, but probably represents a different phenotype. The inflammatory pattern might be neutrophilic, instead of eosinophilic in obese patients with asthma. Allergy is probably not an important factor in the relationship between obesity and asthma.

Therapeutic implications

The main goal of asthma treatment is to achieve adequate control of the disease, as reflected by minimal symptoms and rescue bronchodilator use. Asthma has been reported to be more difficult to control in obese patients compared to individuals with a normal weight[9, 26]. Also the improvement of exhaled nitric oxide levels with inhaled corticosteroid treatment is smaller in obese asthmatics than in lean asthmatics[27]. Is this because they do not respond to inhaled corticosteroids? This could be expected when one assumes that in obese asthmatics it is a neutrophilic instead of eosinophilic airway inflammation. In a recent study by Camargo[28], they found that, compared to subjects with normal BMI, the onset to peak FEV1 may require longer treatment exposure in the very obese.

Could it be that asthma in obese patients is more difficult to control because obese asthmatics have more complaints than lean asthmatics? Although obese asthmatics have the same perceptual responses to bronchoconstriction as lean asthmatics, it is to be expected that they have more complaints of dyspnoea due to their altered lung volumes, as will be discussed later.

Weight reduction from diet and exercise has been found to improve asthma symptoms, but the most striking changes have been reported in morbidly obese asthmatics following bariatric surgery[29-34]. However, these studies are frequently small and underpowered, and are often not designed with a primary outcome or rigorous characterization of asthma. Although there is still only a small body of evidence in favour of the beneficial effect of weight reduction in obese asthmatics, weight reduction does seem to be an important aspect of the treatment of these people.

Hypotheses that may explain the relationship between obesity and asthma

Since obese asthmatics might have a non-allergic phenotype of asthma, there must be another factor explaining the relationship between obesity and asthma. Although there are multiple hypotheses, no causal relationship between obesity and asthma has, as yet, been proven. Even though asthma may promote weight gain through increased sedentary life style and occasional use of oral corticosteroids, this does not fully explain the association of asthma and obesity in the majority of patients. In previous reviews concerning the relationship between obesity and asthma, five hypotheses were put forth (figure 1).

First, obese people consume food with less nutritional value, fewer vitamins and more fat. A high amount of fat intake is associated with asthma[35]. Also zinc- and magnesium deficiencies are associated with asthma and bronchial hyperreactivity (BHR)[36].

Secondly, obesity and asthma may share the same genetic risk factors. This was demonstrated by a large-scale study among 1384 twins, where a strong association between asthma and BMI was found[37].

Co-morbidities, which are a risk factor for asthma as well as obesity, might be the third hypothesis. Obesity, for instance, is a risk factor for gastro-oesophageal reflux disease (GERD) which, in turn, is a risk factor for asthma[38]. The same is true for Obstructive Sleep Apnoea Syndrome (OSAS); the prevalence of OSAS is higher in severe asthma patients as well as in obese patients[39]. A large-scale, questionnaire-based Northern European survey showed that after adjustments for possible confounders, obesity and nocturnal GERD were found to be independent risk factors for the onset of asthma and respiratory symptoms[40].

Fourthly, obesity may alter lung function parameters. Typically, obesity causes a modest reduction in total lung capacity (TLC), and a larger reduction in functional residual capacity (FRC) (figure 2)[41]. The reasons for the reduction in TLC are not known, but they are probably due to a mechanical effect of the adipose tissue. A reduction in the downward movement of the diaphragm, due to increased abdominal mass is likely to decrease TLC by limiting the space for lung expansion on inflation[42]. Furthermore, obese people have a smaller tidal volume and an increased respiration rate with a decreased expiratory reserve volume (ERV)[43]. The FEV1/FVC ratio is usually well preserved

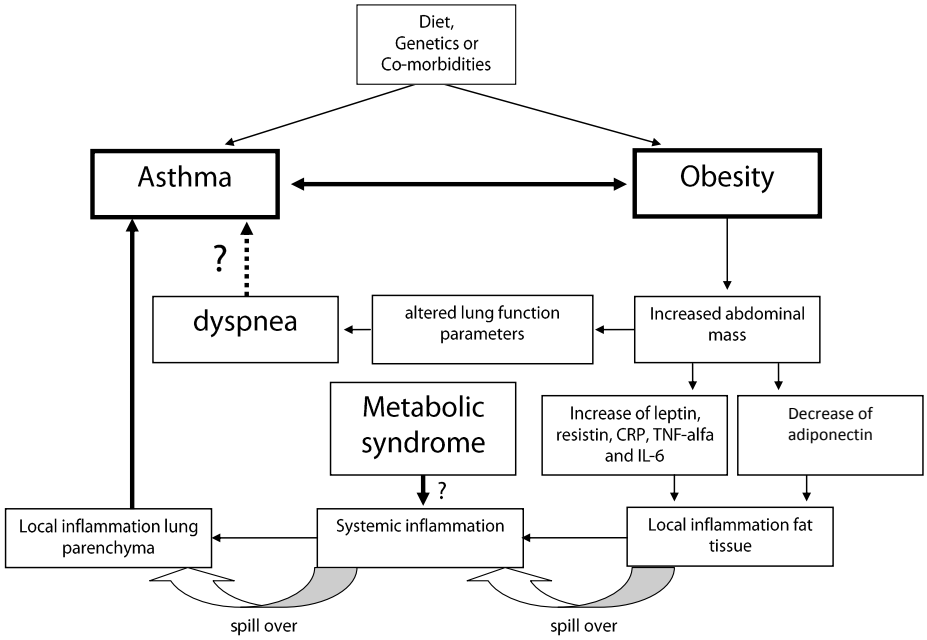

Figure 1 Obesity and asthma relationship
The relationship between obesity and asthma is not yet clear. Diet, genetic factors or comorbidities which give a higher risk for asthma might also give a higher risk for obesity. Obesity gives a greater abdominal mass, which causes altered lung function parameters, which cause dyspnea. Whether or not this dyspnea is asthma is questionable. The abdominal mass also causes a dysbalance in inflammatory proteins, in favour of the pro-inflammatory proteins. This may lead to a local inflammation, which causes a low grade systemic inflammation, which, in turn, causes or enhances a local inflammation of the lung parenchyma.

or increased, which implies that the major effect of obesity is on lung volumes, with no direct effect on airway obstruction. Furthermore, weight loss significantly improves the FRC, TLC and ERV[44].

The decreased lung volume is associated with a decreased diameter of the peripheral airways, which leads to tidal breathing at or near closing volume[41]. Moreover, Bergeron has shown that there is a fat accumulation in the airways in obese patients with less defined cartilage ring[45]. All this can explain why obese patients often have more complaints of dyspnea than subjects with a normal BMI. Salome showed that, although obesity reduces lung volumes, it does not alter sensitivity or maximal response to methacholine in non-asthmatic subjects[46]. Recently, it was also shown that perceptual responses to methacholine-induced bronchoconstriction and lung hyperinflation were similar in obese and normal-weight asthmatics[47]. Thus, obese asthmatics may have more complaints of dyspnea, but this may not be directly related to abnormal airway sensitivity, but may reflect other physiological effects of obesity.

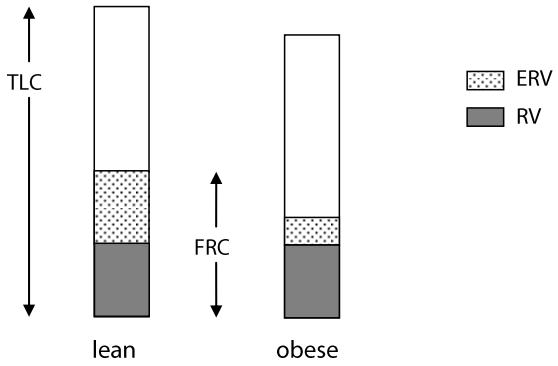

Figure 2 Altered lung function in obesity
Obesity leads to alternations of lung volumes. ERV: expiratory reserve volume; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity

The fifth, and last, hypothesis suggests that systemic inflammation by means of fat-tissue derived adipokines may lead to asthma. The assumption is that inflammatory mediators from the fat tissue come into the systemic circulation, and find their way to the lung parenchyma, where they may cause or intensify airway inflammation .

Obesity is considered to be a state of chronic low-grade systemic inflammation, characterized by a dysbalance of pro- and anti-inflammatory proteins derived from fat tissue cells. Fat tissue was traditionally seen as an organ for storage of energy. Recently, however, it is considered to act as an endocrine organ. The fat tissue is a source of bioactive peptides, which are called adipokines[48]. In 1993, Hotamisligil *et al* discovered that fat cells (adipocytes) in rodents excrete TNF-α. TNF-α is a pro-inflammatory cytokine[49]. Since then, multiple inflammatory peptides have been discovered which have a relationship with obesity. Examples of adipokines are leptin, adiponectin and resistin. Also interleukin (IL)-6 and TNF-α play a role. They are produced by macrophages in the fat tissue.

Leptin (Greek leptos, thin) is excreted by fat tissue and causes the feeling of saturation and increases the metabolism. Moreover, leptin influences the T-cell immunity response and stimulates the proliferation of T-helper cells, which causes increased production of pro-inflammatory cytokines[50]. There is an increased leptin production[51, 52] and a relative leptin resistance in obese patients. A comparison with insulin and insulin resistance can be made: here the primary reaction of the body is to increase the production of insulin so that the same physical result is achieved. The leptin concentration is not only increased in obesity, but also in asthma[53, 54].

Obesity is associated with necrosis of the adipocytes, causing the interstitium to be exposed to little fat drops. Macrophages will collect around this necrotizing adipocytes and become active. These macrophages will produce TNF-α and IL-6, which will cause a decrease in local production of adiponectin[55]. Adiponectin is an insulin-regulating hormone. It also has anti-inflammatory effects: it decreases the production of pro-

inflammatory cytokines and it increases the production of IL-10 and IL-1. Plasma adiponectin levels are reversely correlated to BMI[56], but there is no clear relationship between adiponectin and asthma[57-60].

Xu *et al.*[61]have been able to show in a mice model that there is histological evidence for a significant infiltration of macrophages in the fat tissue of obese mice. Moreover, they also have shown that many inflammatory and specific macrophage genes are dramatically upregulated in the fat tissue. This suggests that macrophages in the fat tissue play an active role in obesity and macrophage-related inflammation. Weisberg *et al.*[62] showed that the macrophages are responsible for almost all expression of TNF-α and IL-6 in the fat tissue. TNF-α is a potent pro-inflammatory cytokine and is involved in many processes in the human body, in particular inflammation, cell proliferation, cell differentiation, apoptosis and fat metabolism. IL-6 regulates the production of the strong pro-inflammatory protein C-reactive protein (CRP).

In summary, in animal models the influence of the different adipokines associated with obesity seem to have an effect on the airway inflammation. In humans, however, the association is not yet confirmed. Further studies are needed to investigate whether a dysbalance in pro and anti-inflammatory cytokines in the systemic circulation may induce a change in concentration of the same cytokines in the lung tissue. This may result in an increased airway inflammation.

Metabolic syndrome

The fact that asthma improves after weight loss either with bariatric surgery or low caloric diet supports the relation between obesity and asthma. Moreover, Cottam found that obesity was manifested by a chronic inflammation (including elevation of monocytes and eosinophils), which appeared to be reversible within 6 months after bariatric surgery[63]. Also, weight loss by low-energy diet was associated with a reduction in markers of systemic inflammation[64, 65]. So the hypothesis that the relationship between obesity and asthma is based on a systemic inflammation seems quite plausible. The metabolic syndrome might contribute to this low-grade systemic inflammation.

Recently, the metabolic syndrome has been postulated as a new hypothesis which might explain the relationship between obesity and asthma. Obesity, and mainly central obesity, is an important component of the metabolic syndrome. The metabolic syndrome is a term to cluster type 2 diabetes mellitus, hypertension, dyslipidemia and central obesity (table 2).

Table 2 Metabolic syndrome

Risk factor	Objective
Abdominal obesity (waist circumference)	
- male	> 102 cm
- female	> 88 cm
Triglycerides	>1,7 mmol/l or treatment for hypertriglyceraemia
HDL-cholesterol	
- male	<1,03 mmol/l, or treatment for low HDL-C
- female	< 1,3 mmol/l or treatment for low HDL-C
Blood pressure	≥130/≥85 mmHg, or treatment for hypertension
Blood glucose (plasma)	≥ 6,1 mmol/l, or treatment for hyperglycaemia

Definition of the metabolic syndrome according to NCEP-ATPIII criteria on basis of clinical characteristics. Metabolic syndrome when 3 out of 5 characteristics.

Leone found an independent relationship between lung function impairment (FEV1 or FVC < lower limit of normal) and metabolic syndrome in both sexes, predominantly due to abdominal obesity[66]. Lee *et al*[67] found that the metabolic syndrome was associated with asthma symptoms. The evidence for the relationship between metabolic syndrome and asthma is scarce, mainly because it is a new idea. More research is needed to make a definitive conclusion.

The metabolic syndrome is a way to group different diseases. If there might be a relationship between the metabolic syndrome and asthma, there might also be a relationship between the separate compounds of the metabolic syndrome and asthma. In a cross-sectional population-based study, obesity and insulin resistance were associated with an increased risk of aeroallergen sensitization and asthma (allergic and non-allergic)[68]. Thuesen[69] found, in a recent population-based, prospective study among 1443 adults, that insuline-resistance is a stronger risk factor for asthma symptoms than obesity. Hyperglycemia itself may not be the important factor. Shore *et al* have demonstrated in lean wild-type and leptin receptor-deficient, diabetic, obese mice that administration of metformin did not affect ozone-induced airway inflammation[70].

More research is needed to see whether the metabolic syndrome, or it separate components, are the "missing link" between obesity and asthma. Also here the same remarks as for the fat tissue derived adipokines can be made. If it is so that the metabolic syndrome contributes to the low grade systemic inflammation, the question remains whether this low grade systemic inflammation has its local effects on the lung parenchyma. And whether this systemic inflammation causes or enhances the bronchial inflammation.

Critical notes

Many of the articles discussed in this review are epidemiologic studies among patients with asthma, where asthma is defined as either physician-diagnosed or self-reported. Very few studies performed (extensive) lung function tests to confirm the diagnosis of asthma. Often the diagnosis is based on symptoms and medication use. The question is whether these patients truly have asthma. In a retrospective study among children, a strong correlation was found between general practitioner and specialist diagnosed asthma, irrespective of BMI[71]. In an extensive study among adult patients, the diagnosis of asthma was revisited. In 31.8% of the obese, and 28.7% of the non-obese group (p=0.46) the diagnosis of asthma was rejected. The percentage of misdiagnosis is the same in the obese and non-obese group, so the relationship between asthma and obesity cannot be explained by the fact that there is an overdiagnosis of asthma in the obese population[72]. In a recent study Pakhale *et al*[73] found a misdiagnosis of asthma in up to 30% of patients. They used a rigorous diagnostic testing algorithm to confirm the diagnosis of asthma. They found that misdiagnosis of asthma was associated with gender, a recent diagnosis, older age and increased FEV_1, but not with obesity. Also, obese subjects who made urgent healthcare visits for respiratory symptoms were more likely to be misdiagnosed with asthma. It is possible that these symptoms could be the result of increased effort in breathing associated with obesity, rather than airway inflammation or airway hyperresponsiveness.

Another disadvantage of most studies is that they are based on self-reported weight. A BMI based on self-reported height and weight is not accurate for either children or adults[74]. The weight will be underreported, and the length overreported. There is however, an algorithm to correct for this.

Some previous studies of the association of adiposity and lung function have used only BMI as a marker of obesity, without taking body composition and fat distribution into account. The waist circumference - or even better, a MRI-based visceral fat quantification - is possibly a more accurate measure than BMI. The distribution of body fat may be an important determinant of lung function, and this may account for the more pronounced association between central adiposity and obstructive lung function in men as compared to women[75]. Steele *et al.* performed a study to examine the relationship among body fatness, fat distribution, and lung function, adjusted for physical activity, energy expenditure and aerobic fitness[76]. They found that obesity is inversely associated with lung function (FEV_1 and FVC) in adults. Central fat distribution, however, appears to have a stronger relationship to respiratory mechanics (FEV_1) in men than in women. These associations were independent of the degree of physical activity in this cohort.

CONCLUSION

From the literature discussed, it can be concluded that there is a relationship between obesity and asthma. "Obese asthma" may be a unique phenotype of asthma, characterized by decreased lung volumes, greater symptoms for a given degree of lung function impairment, destabilization or lack of asthma control, lack of eosinophilic inflammation and a different response to controller medication. Therefore, the clinical evaluation of an obese patient with asthma must require a more rigorous and objective approach.

Whether this relationship is really causal or represents parallel co-morbidities is unclear. In animal models, there is an increasing amount of evidence for the role of adipokines derived from fat tissue in the relationship between obesity and asthma. This adipokines cause a low grade systemic inflammation, which might cause or enhance bronchial inflammation. The data are conflicting in humans. However, the fact that weight loss improves asthma control and normalizes the concentration of adipokines in the serum implies that there must be some role for adipokines in the relationship between obesity and asthma.

Since obesity is a component of the metabolic syndrome and the metabolic syndrome is also a form of systemic inflammation, it is to be expected that there is a relationship between metabolic syndrome and asthma. The few data that are available show that there is no relationship between metabolic syndrome and asthma, but there is one between the metabolic syndrome and asthma-like symptoms.

Further research is needed to confirm the relationship between obesity and asthma in humans, where a rigorous approach in the diagnosis of asthma and use of good control groups is essential. Intervention-based longitudinal research might find a definitive answer to the question of what the basis of the relationship between obesity and asthma could be.

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REFERENCES

1. Organisation WH. Obesity and overweight, fact sheet No 311. 2006 [cited; Available from: http://www.who.int/mediacentre/factsheets/fs311/en/print.html
2. James AL, Knuiman MW, Divitini ML, Hui J, Hunter M, Palmer LJ, Maier G, Musk AB. Changes in the prevalence of asthma in adults since 1966: the Busselton health study. *Eur Respir J* 2010;35(2):273-8.
3. Chen Y, Rennie D, Cormier Y, Dosman J. Atopy, obesity, and asthma in adults: the Humboldt study. *J Agromedicine* 2009;14(2):222-7.
4. Taylor B, Mannino D, Brown C, Crocker D, Twum-Baah N, Holguin F. Body mass index and asthma severity in the National Asthma Survey. *Thorax* 2008;63(1):14-20.
5. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;175(7):661-6.
6. Camargo CA, Jr., Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;159(21):2582-8.
7. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med* 2006;100(4):648-57.
8. Saint-Pierre P, Bourdin A, Chanez P, Daures JP, Godard P. Are overweight asthmatics more difficult to control? *Allergy* 2006;61(1):79-84.
9. Clerisme-Beaty EM, Karam S, Rand C, Patino CM, Bilderback A, Riekert KA, Okelo SO, Diette GB. Does higher body mass index contribute to worse asthma control in an urban population? *J Allergy Clin Immunol* 2009;124(2):207-12.
10. Mosen DM, Schatz M, Magid DJ, Camargo CA, Jr. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol* 2008;122(3):507-11 e6.
11. Akerman MJ, Calacanis CM, Madsen MK. Relationship between asthma severity and obesity. *J Asthma* 2004;41(5):521-6.
12. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005;171(4):334-9.
13. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178(3):218-24.
14. Lugogo NL, Kraft M, Dixon AE. Does Obesity Produce a Distinct Asthma Phenotype? *J Appl Physiol* 2010;108(3):729-34.
15. De Winter-de Groot KM, Van der Ent CK, Prins I, Tersmette JM, Uiterwaal CS. Exhaled nitric oxide: the missing link between asthma and obesity? *J Allergy Clin Immunol* 2005;115(2):419-20.
16. Kazaks A, Uriu-Adams JY, Stern JS, Albertson TE. No significant relationship between exhaled nitric oxide and body mass index in people with asthma. *J Allergy Clin Immunol* 2005;116(4):929-30; author reply 930.
17. Todd DC, Armstrong S, D'Silva L, Allen CJ, Hargreave FE, Parameswaran K. Effect of obesity on airway inflammation: a cross-sectional analysis of body mass index and sputum cell counts. *Clin Exp Allergy* 2007;37(7):1049-54.
18. Sutherland TJ, Cowan JO, Young S, Goulding A, Grant AM, Williamson A, Brassett K, Herbison GP, Taylor DR. The association between obesity and asthma: interactions between systemic and airway inflammation. *Am J Respir Crit Care Med* 2008;178(5):469-75.
19. van Veen IH, Ten Brinke A, Sterk PJ, Rabe KF, Bel EH. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. *Allergy* 2008;63(5):570-4.

20. Calixto M, Lintomen L, Schenka A, Saad MJ, Zanesco A, Antunes E. Obesity enhances eosinophilic inflammation in a murine model of allergic asthma. *Br J Pharmacol* 2013;159(3):617-25.
21. Hancox RJ, Milne BJ, Poulton R, Taylor DR, Greene JM, McLachlan CR, Cowan JO, Flannery EM, Herbison GP, Sears MR. 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(5):440-5.
22. Schachter LM, Peat JK, Salome CM. Asthma and atopy in overweight children. *Thorax* 2003;58(12): 1031-5.
23. Chen Y, Dales R, Jiang Y. The association between obesity and asthma is stronger in nonallergic than allergic adults. *Chest* 2006;130(3):890-5.
24. Jarvis D, Chinn S, Potts J, Burney P. Association of body mass index with respiratory symptoms and atopy: results from the European Community Respiratory Health Survey. *Clin Exp Allergy* 2002;32(6):831-7.
25. Loerbroks A, Apfelbacher CJ, Amelang M, Sturmer T. Obesity and adult asthma: potential effect modification by gender, but not by hay fever. *Ann Epidemiol* 2008;18(4):283-9.
26. Camargo CA, Jr., Sutherland ER, Bailey W, Castro M, Yancey SW, Emmett AH, Stempel DA. 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(7):1629-35.
27. Sutherland ER, Lehman EB, Teodorescu M, Wechsler ME. Body mass index and phenotype in subjects with mild-to-moderate persistent asthma. *J Allergy Clin Immunol* 2009;123(6):1328-34 e1.
28. Camargo CA, Jr., Boulet LP, Sutherland ER, Busse WW, Yancey SW, Emmett AH, Ortega HG, Ferro TJ. Body mass index and response to asthma therapy: fluticasone propionate/salmeterol versus montelukast. *J Asthma*;47(1):76-82.
29. Aaron SD, Fergusson D, Dent R, Chen Y, Vandemheen KL, Dales RE. Effect of weight reduction on respiratory function and airway reactivity in obese women. *Chest* 2004;125(6):2046-52.
30. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *Bmj* 2000;320(7238):827-32.
31. Eneli IU, Skybo T, Camargo CA, Jr. Weight loss and asthma: a systematic review. *Thorax* 2008;63(8):671-6.
32. Dixon JB, Chapman L, O'Brien P. Marked improvement in asthma after Lap-Band surgery for morbid obesity. *Obes Surg* 1999;9(4):385-9.
33. Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. *Chest* 2000;118(5):1315-21.
34. Nguyen NT, Hinojosa MW, Smith BR, Gray J, Varela E. Improvement of restrictive and obstructive pulmonary mechanics following laparoscopic bariatric surgery. *Surg Endosc* 2009;23(4):808-12.
35. Weiss ST. Obesity: insight into the origins of asthma. *Nat Immunol* 2005;6(6):537-9.
36. Tantisira KG, Weiss ST. Complex interactions in complex traits: obesity and asthma. *Thorax* 2001; 56 Suppl 2:ii64-73.
37. Hallstrand TS, Fischer ME, Wurfel MM, Afari N, Buchwald D, Goldberg J. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. *J Allergy Clin Immunol* 2005; 116(6):1235-41.
38. Kiljander TO, Harding SM, Field SK, Stein MR, Nelson HS, Ekelund J, Illueca M, Beckman O, Sostek MB. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2006;173(10):1091-7.
39. Julien JY, Martin JG, Ernst P, Olivenstein R, Hamid Q, Lemiere C, Pepe C, Naor N, Olha A, Kimoff RJ. Prevalence of obstructive sleep apnea-hypopnea in severe versus moderate asthma. *J Allergy Clin Immunol* 2009;124(2):371-6.

40. Gunnbjornsdottir MI, Omenaas E, Gislason T, Norrman E, Olin AC, Jogi R, Jensen EJ, Lindberg E, Bjornsson E, Franklin K, Janson C, Gulsvik A, Laerum B, Svanes C, Toren K, Tunsater A, Lillienberg L, Gislason D, Blondal T, Bjornsdottir US, Jorundsdottir KB, Talvik R, Forsberg B, Franklin K, Lundback B, Soderberg M, Ledin MC, Boman G, Norback D, Wieslander G, Spetz-Nystrom U, Cashelunge KS, Ryden E. Obesity and nocturnal gastro-oesophageal reflux are related to onset of asthma and respiratory symptoms. *Eur Respir J* 2004;24(1):116-21.
41. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med* 2006;174(2):112-9.
42. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol* 2010;108(1):206-11.
43. Beuther DA. Obesity and asthma. *Clin Chest Med* 2009;30(3):479-88.
44. Weiner P, Waizman J, Weiner M, Rabner M, Magadle R, Zamir D. Influence of excessive weight loss after gastroplasty for morbid obesity on respiratory muscle performance. *Thorax* 1998;53(1): 39-42.
45. Bergeron C, Boulet LP, Hamid Q. Obesity, allergy and immunology. *J Allergy Clin Immunol* 2005; 115(5):1102-4.
46. Salome CM, Munoz PA, Berend N, Thorpe CW, Schachter LM, King GG. Effect of obesity on breathlessness and airway responsiveness to methacholine in non-asthmatic subjects. *Int J Obes (Lond)* 2008;32(3):502-9.
47. Deesomchok A, Fisher T, Webb KA, Ora J, Lam YM, Lougheed MD, O'Donnell DE. Effects of Obesity on Perceptual and Mechanical Responses to Bronchoconstriction in Asthma. *Am J Respir Crit Care Med* 2009.
48. Ronti T, Lupattelli G, Mannarino E. The endocrine function of adipose tissue: an update. *Clin Endocrinol (Oxf)* 2006;64(4):355-65.
49. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 1993;259(5091):87-91.
50. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* 1998;394(6696): 897-901.
51. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;334(5):292-5.
52. Couillard C, Mauriege P, Imbeault P, Prud'homme D, Nadeau A, Tremblay A, Bouchard C, Despres JP. Hyperleptinemia is more closely associated with adipose cell hypertrophy than with adipose tissue hyperplasia. *Int J Obes Relat Metab Disord* 2000;24(6):782-8.
53. Guler N, Kirerleri E, Ones U, Tamay Z, Salmayenli N, Darendeliler F. Leptin: does it have any role in childhood asthma? *J Allergy Clin Immunol* 2004;114(2):254-9.
54. Mai XM, Bottcher MF, Leijon I. Leptin and asthma in overweight children at 12 years of age. *Pediatr Allergy Immunol* 2004;15(6):523-30.
55. Bruun JM, Lihn AS, Verdich C, Pedersen SB, Toubro S, Astrup A, Richelsen B. Regulation of adiponectin by adipose tissue-derived cytokines: in vivo and in vitro investigations in humans. *Am J Physiol Endocrinol Metab* 2003;285(3):E527-33.
56. Engeli S, Feldpausch M, Gorzelniak K, Hartwig F, Heintze U, Janke J, Mohlig M, Pfeiffer AF, Luft FC, Sharma AM. Association between adiponectin and mediators of inflammation in obese women. *Diabetes* 2003;52(4):942-7.
57. Kim KW, Shin YH, Lee KE, Kim ES, Sohn MH, Kim KE. Relationship between adipokines and manifestations of childhood asthma. *Pediatr Allergy Immunol* 2008;19(6):535-40.

58. Sutherland TJ, Sears MR, McLachlan CR, Poulton R, Hancox RJ. Leptin, adiponectin, and asthma: findings from a population-based cohort study. *Ann Allergy Asthma Immunol* 2009;103(2):101-7.
59. Sood A, Cui X, Qualls C, Beckett WS, Gross MD, Steffes MW, Smith LJ, Jacobs DR, Jr. Association between asthma and serum adiponectin concentration in women. *Thorax* 2008;63(10):877-82.
60. Jartti T, Saarikoski L, Jartti L, Lisinen I, Jula A, Huupponen R, Viikari J, Raitakari OT. Obesity, adipokines and asthma. *Allergy* 2009;64(5):770-7.
61. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003;112(12):1821-30.
62. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003;112(12):1796-808.
63. Cottam DR, Schaefer PA, Shaftan GW, Velcu L, Angus LD. Effect of surgically-induced weight loss on leukocyte indicators of chronic inflammation in morbid obesity. *Obes Surg* 2002;12(3):335-42.
64. Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, Giugliano D. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *Jama* 2003;289(14):1799-804.
65. Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, Vidal H, Hainque B. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *J Clin Endocrinol Metab* 2000;85(9):3338-42.
66. Leone N, Courbon D, Thomas F, Bean K, Jego B, Leynaert B, Guize L, Zureik M. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med* 2009;179(6):509-16.
67. Lee EJ, In KH, Ha ES, Lee KJ, Hur GY, Kang EH, Jung KH, Lee SY, Kim JH, Lee SY, Shin C, Shim JJ, Kang KH, Yoo SH. Asthma-like symptoms are increased in the metabolic syndrome. *J Asthma* 2009; 46(4):339-42.
68. Husemoen LL, Glumer C, Lau C, Pisinger C, Morch LS, Linneberg A. Association of obesity and insulin resistance with asthma and aeroallergen sensitization. *Allergy* 2008;63(5):575-82.
69. Thuesen BH, Husemoen LL, Hersoug LG, Pisinger C, Linneberg A. Insulin resistance as a predictor of incident asthma-like symptoms in adults. *Clin Exp Allergy* 2009;39(5):700-7.
70. Shore SA, Williams ES, Zhu M. No effect of metformin on the innate airway hyperresponsiveness and increased responses to ozone observed in obese mice. *J Appl Physiol* 2008;105(4):1127-33.
71. Lang JE, Feng H, Lima JJ. Body mass index-percentile and diagnostic accuracy of childhood asthma. *J Asthma* 2009;46(3):291-9.
72. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Doucette S, Fergusson D. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179(11):1121-31.
73. Pakhale S, Doucette S, Vandemheen K, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Aaron SD. A comparison of obese and nonobese asthmatics: Exploring an asthma-obesity interaction. *Chest* 2010;137(6):1316-1323.
74. Gorber SC, Tremblay M, Moher D, Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev* 2007;8(4):307-26.
75. Harik-Khan RI, Wise RA, Fleg JL. The effect of gender on the relationship between body fat distribution and lung function. *J Clin Epidemiol* 2001;54(4):399-406.
76. Steele RM, Finucane FM, Griffin SJ, Wareham NJ, Ekelund U. Obesity is associated with altered lung function independently of physical activity and fitness. *Obesity (Silver Spring)* 2009;17(3):578-84.

4

Systemic inflammation and lung function impairment in morbidly obese subjects with the metabolic syndrome

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ABSTRACT

Background: Obesity and asthma are associated. There is a relationship between lung function impairment and the metabolic syndrome. Whether this relationship also exists in the morbidly obese is still unknown.

Hypothesis: Low grade systemic inflammation associated with the metabolic syndrome causes inflammation in the lungs, and hence lung function impairment.

Methods: Cross-sectional study of morbidly obese patients undergoing pre-operative screening for bariatric surgery. Metabolic syndrome was assessed according to the revised NCEP-ATP III criteria.

Results: 452 patients were included. Patients with the metabolic syndrome (n=293) had significantly higher blood monocyte (mean 5.3 versus 4.9, p=0.044) and eosinophil percentages (median 1.0 versus 0.8, p=0.002) while the total leukocyte count did not differ between the groups. The FEV_1/FVC ratio was significantly lower in patients with the metabolic syndrome (76.7% versus 78.2%, p=0.032). Blood eosinophils were associated with FEV1/FVC ratio (adj. B -0.113, p=0.018).

Conclusion: Although the difference in FEV1/FVC ratio between the groups is relatively small, in this cross-sectional study, and its clinical relevance may be limited, these data indicate that the presence of the metabolic syndrome may influence lung function impairment, through the induction of relative eosinophilia.

INTRODUCTION

Obesity is an increasing worldwide problem that has taken on epidemic proportions[1]. Cross-sectional studies have shown a positive association between obesity and asthma[2]. Weight loss in obese asthma patients improved morbidity and lung function[3], however, the mechanisms underlying the relationship between asthma and obesity are unclear. It is suggested that low grade systemic inflammation associated with obesity plays a role.

The metabolic syndrome is a common metabolic disorder that may result from the increasing prevalence of obesity. Metabolic syndrome is a cluster of cardiometabolic risk factors characterized by abdominal obesity, insulin resistance and chronic systemic inflammation[4]. Positive associations with lung function impairment have been reported for components of the metabolic syndrome, such as hypertension[5], type diabetes mellitus[6, 7], low-density lipoprotein cholesterol[8] and overall obesity[9]. In recent large cohort studies it has been shown that there is also a relationship between lung function impairment and the metabolic syndrome[10-12]. However, all aforementioned studies included overweight as well as normal weight subjects and were therefore not specifically targeted to examine these issues in the morbidly obese. Data on the association between lung function impairment and the metabolic syndrome in the morbidly obese are limited.

The mechanisms underlying the relationship between impaired lung function and the metabolic syndrome are unclear. The chronic low-grade systemic inflammation that is associated with obesity might explain this relationship. Our hypothesis is that this low-grade systemic inflammation causes inflammation in the lungs, and hence lung function impairment.

We therefore performed a study to investigate (1) the association between lung function and the metabolic syndrome in morbidly obese subjects, and (2) to determine the effect of systemic inflammation on the relationship between lung function impairment and the metabolic syndrome.

METHODS

Study population

The subjects included in this study were consecutive patients who underwent preoperative screening for bariatric surgery in the Sint Franciscus Gasthuis in Rotterdam, the Netherlands, between October 2009 and May 2011. Eligibility criteria for bariatric surgery were: age between 18 and 60 years, either body mass index (BMI) ≥ 40 kg/m^2 or ≥ 35 kg/m^2 combined with the presence of comorbidity e.g. diabetes mellitus, hypertension or proven obstructive sleep apnea syndrome (OSAS). Subjects underwent baseline

physical examinations that included routine assessment of anthropometry, blood pressure, pulmonary function and blood samples.

Height and weight were measured wearing light clothes and no shoes. Body mass index was calculated as weight (in kg) divided by height (in m) squared. Abdominal circumference was measured directly to the body surface midway between the lower rib margin and the ileac crest.

The Epworth Sleepiness Scale questionnaire[13] was used to assess OSAS, and the GERD-Questionnaire[14] for gastro-esophageal reflux disease (GERD).

All subjects gave informed consent and the local ethics committee (Toetsingscommissie Wetenschappenlijk Onderzoek Rotterdam e.o, trialnumber NL25637.101.08) approved the study protocol (Netherlands Trial Register number NTR3204).

Definition of the metabolic syndrome

Metabolic syndrome was diagnosed according to the National Cholesterol Education Program's Adult Treatment Panel III report (NCEP ATP-III) criteria when ≥3 of the following 5 risk factors were present: abdominal obesity, an elevated level of serum triglycerides, low serum level of high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and high serum glucose level or treatment for any of these disorders[4].

Pulmonary function tests

Spirometry was performed with Vmax spirometer (Vmax SensorMedics Viasys, type Encore 20/22/229/62 Encore, Cardinal Health, USA) before and after 400 µg of inhaled salbutamol, with subjects in a sitting position and nose clips in place according to the American Thoracic Society / European Respiratory Society statement[15]. All values obtained were related to height, age and gender and expressed as percentage of their predicted value (reference ERS 1993). The pulmonary function results are prebronchodilator values unless specifically noted. Exhaled Nitric Oxide (Fe_{NO}) was measured with Niox mino (Aerocrine, Sweden) and expressed in parts per billion (ppb).

Clinical chemistry

Blood was taken by venapuncture during routine pre-operative screening. Laboratory measurements were performed according to standard procedures by our department of Clinical Chemistry. Plasma-cholesterol, HDL-cholesterol, glucose, triglycerides and CRP were measured using LX 20 and DxC analyzers (Beckman Coulter, Miami, FL, USA). LDL-cholesterol was calculated using the Friedewald formula. Total IgE and specific plasma IgE were determined with a solid-phase two-step chemiluminescent immunoassay on the Immulite 2000 (Siemens, Los Angeles, CA). A positive inhalation screen was defined as at least one increased amount of specific IgE against one of the following allergens; Aspergillus fumigatus, house-dust mite, cat, dog, grass, birch or herbs. Blood cell counts

and 5-part leukocyte differentiation were determined automatically using LH750 analyzers (Beckman Coulter). HbA1C was determined using a Tosoh G8 HLC-723 analyzer (Tosoh Bioscience, Tokyo, Japan). Insulin was measured using radio immunoassay (RIA) DSL1600 (Diagnostic Systems Laboratories, Webster, Tx, USA). Vitamin D was determined by RIA or chemiluminescence (LIA) on Liason analyzers (DiaSorin, Stillwater, MN, USA).

Statistical analyses

Unadjusted between-group comparisons were performed using Student's t test or the Chi-square test, where appropriate, and Mann Whitney U test for nonparametric comparisons (eosinophils). CRP, IgE, insulin, lipoprotein-a and vitamin B6 were not normally distributed (standard error of kurtosis and skewness below -3 or above 3), and were therefore log-transformed. Univariate linear regression was used to evaluate associations between continuous variables. Backward linear regression analysis was used to investigate which component of the metabolic syndrome is related to the FEV_1/FVC ratio. Variables associated with FEV_1/FVC ratio in univariate analysis at a p-value of <0.1 were examined in the multiple linear regression analysis. Since the FEV_1/FVC ratio as percentage predicted is already corrected for height, age and gender we did not add these variables to the model. As eosinophils and abdominal circumference were correlated, we selected only eosinophils to prevent collinearity. We omitted OSAS because of the large proportion of missing data. All analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, Illinois, USA). Results were evaluated at 95% confidence interval at a two-sided $p<0.05$.

RESULTS

Subjects

452 subjects were included in the study (97 males and 355 females). 293 subjects (64.8%) fulfilled the criteria for metabolic syndrome. Table 1 shows the general characteristics of the study population. Patients with the metabolic syndrome were significantly older (mean 43 years), were less often female (73.7%), and had a larger abdominal circumference in centimeters (mean 134.3 cm) compared to patients without the metabolic syndrome (mean 37 years, 87.4% and mean 126.8 cm, respectively).

Metabolic syndrome and blood parameters

Patients with the metabolic syndrome did not have a higher total leukocyte count or neutrophil percentage in the peripheral blood ($p=0.253$), but they did have a significantly higher percentage of eosinophils ($p=0.002$) and monocytes ($p=0.044$) compared to patients without the metabolic syndrome (Table 2). Other parameters of systemic

Table 1 General characteristics of the population included in the study

	No metabolic syndrome (n=159)	Metabolic syndrome (n=293)	p Value
Age (years)	37 ± 11	43 ± 10	<0.001[1]
BMI (kg/m^2)	45.4 ± 6.7	46.0 ± 6.5	0.395
Gender (% female)	87.4%	73.7%	0.001[2]
Ethnicity (% Caucasian)	80.5%	85.0%	0.222
Smoking			
%never smoked,	49%	40%	0.152
%stopped smoking,	29%	32%	
%smokes	22%	28%	
Pack years [3]	6.0 ± 11.2	9.9 ± 14.8	0.003
Abdominal circumference (cm)	126.8 ± 14	134.3 ± 16	<0.001
Systolic blood pressure (mmHg)	136.4 ± 17.9	145.98 ± 16.6	<0.001
Diastolic blood pressure (mmHg)	83.6 ± 11.8	87.83 ± 10.1	<0.001
Comorbidities			
Diabetes mellitus	3.8%	30.3%	<0.001
Hypertension	18.9%	42.8%	<0.001
Hypercholesterolemia	1.9%	21.7%	<0.001
Self reported asthma	19.6%	21.0%	0.723
Use of inhaled corticosteroids	3.8%	5.5%	0.413

[1] Data presented as mean ± standard deviation, p-value for Student's t test
[2] Data presented as percentage, p-value for Chi-square test
[3] Data were log transformed for statistical analysis

inflammation such as CRP, Complement C3 and Complement C4 did not show significant differences between the two groups (Table 2). There was no correlation between BMI and eosinophils. We did find a low, but significant correlation between eosinophils and abdominal circumference (Spearman correlation coefficient 0.270, p<0.001), and CRP and abdominal circumference (Spearman correlation coefficient 0.146, p=0.010).

Metabolic syndrome and pulmonary function tests

The subjects with the metabolic syndrome showed a significantly lower FEV_1/FVC ratio – a measure for bronchial obstruction - compared to the group without the metabolic syndrome (76.7% and 78.2% respectively, p=0.032), while no difference was observed regarding FEV_1 or FVC (Table 3). Although there was no significant difference in FEF_{25-75} between subjects with and without the metabolic syndrome, the FEF_{75} was significant lower in the metabolic syndrome group (p=0.036). Log transformed Fe_{NO} – a measure for bronchial inflammation - showed no difference between the two groups. There was no correlation between BMI and Fe_{NO}, and abdominal circumference and Fe_{NO}.

Table 2 Comparison of blood parameters between subjects with and without metabolic syndrome

	No metabolic syndrome (n=159)	Metabolic syndrome (n=293)	p Value
Leukocytes (10^9/L)	8.6 ± 2.3	8.9 ± 2.1	0.253[1]
Neutrophils (%)	70.1 ± 8.6	68.9 ± 9.1	0.186
Lymphocytes (%)	23.7 ± 7.1	23.8 ± 7.0	0.844
Monocytes (%)	4.9 ± 1.8	5.3 ± 1.9	0.044
Eosinophils (%)	0.82 (0.05-1.07)	1.00 (0.45-1.85)	0.002[2]
CRP (mg/L) [3]	9.6 ± 7.4	9.5 ± 8.0	0.865
Cholesterol (mmol/l)	5.2 ± 1.0	5.1 ± 1.1	0.198
HDL- cholesterol (mmol/l)	1.3 ± 0.3	1.1 ± 0.2	<0.001
LDL- cholesterol (mmol/l)	3.5 ± 0.9	3.3 ± 1.1	0.108
Triglyceride (mmol/l)	1.0 ± 0.4	1.6 ± 1.0	<0.001
Glucose (mmol/l)	6.3 ± 1.3	8.2 ± 3.9	<0.001
HbA1C (%)	5.52± 0.4	6.4 ± 1.5	<0.001
Insulin (mE/L) [3]	56.2 ± 58.1	75.0 ± 79.4	<0.001
Vitamin D (nmol/L)	39.5 ± 22.9	38.5 ± 17.7	0.661
IgE (kU/L) [3]	213.5 ± 479.9	197.8 ± 391.3	0.141
Positive inhalation screen	46.2%	44.0%	0.694

[1] Data presented as mean ± standard deviation, p-value for Student's t-test
[2] Data presented as median (1^{st}-3^{rd} quartiles), p-value for Mann-Whitney U test
[3] Data were log transformed for statistical analysis

Subgroup analysis – self reported asthma

There was no difference in the prevalence of self reported asthma between subjects with or without the metabolic syndrome (21.0% versus 19.6% respectively, p=0.723). In a subgroup analysis of subjects with self reported asthma, we found no significant difference in the use of inhaled corticosteroids, body mass index, pack years, FEV_1 (% predicted), FEV_1/FVC (% predicted), Fe_{NO}, blood eosinophils or CRP between subjects with or without the metabolic syndrome (data not shown).

Subgroup analysis – reversibility

In a subgroup analysis of subjects with and without reversibility ($\Delta FEV_1 \geq 12\%$), we found that only 50% of subjects with reversibility (n=30) had self reported asthma. Although subjects with reversibility did use more often inhaled corticosteroids (13.3% versus 4.4%, p=0.032), there was no significant difference in Fe_{NO}, blood eosinophils or CRP between subjects with and without the metabolic syndrome.

Table 3 Pulmonary function test of subjects with and without metabolic syndrome

	No metabolic syndrome (n=159)	Metabolic syndrome (n=293)	p Value
FEV_1 (% predicted)	93.0 ± 13.9	91.2 ± 14.5	0.206[3]
FVC (% predicted)	100.6 ± 14.0	98.5 ± 14.7	0.206
FEV_1/FVC	78.2 ± 6.9	76.7 ± 6.4	0.032
FEF_{25-75} (% predicted)	77.4 ± 24.0	73.9 ± 23.3	0.152
Reversibility FEV_1 >12%	6%	7%	0.523[2]
Fe_{NO} (ppb) [1]	19.3 ± 22.4	17.6 ± 12.6	0.541

[1] Data were log transformed before comparison

[2] Data presented as percentage, p-value for Chi-square analysis,

[3] Data presented as mean ± standard deviation, p values for Student T-test

FEV_1, forced expired volume in 1 second; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow 25%-75%; Fe_{NO}, fractional expiratory nitric oxide; TLC, total lung capacity.

Variables related with FEV_1/FVC ratio

Since the FEV_1/FVC ratio was the only variable of spirometric function tests which was different between subjects with and without the metabolic syndrome, and our hypothesis was that the metabolic syndrome causes a lower FEV_1/FVC ratio – and not the other way around - we investigated which variables were related to the FEV_1/FVC ratio.

There was an association between the peripheral blood eosinophils percentage and the FEV_1/FVC ratio (univariate linear regression coefficient= -0.806, p=0.006). Abdominal circumference and OSAS (Eppworth Sleepiness Scale (ESS)) were significantly related to the FEV_1/FVC ratio (univariate linear regression analysis), whereas BMI, GERD, CRP and monocytes were not significantly related to the FEV_1/FVC ratio (table 4). Missing values of ESS were not correlated to other variables.

Since the metabolic syndrome was associated with the FEV_1/FVC ratio, we investigated which of the components of the metabolic syndrome contributed to this relationship. Only hypertension was significantly related to FEV_1/FVC ratio (regression coefficient = -1.612, p=0.038 in backward linear regression analysis) (Table 5).

Multiple regression analysis

After correction for the use of inhaled corticosteroids, and the number of pack years, we found an association between blood eosinophils and the FEV_1/FVC ratio (adj. B -0.113, p=0.018) (table 6).

DISCUSSION

This study shows that obese patients with the metabolic syndrome have a higher proportion of blood monocytes and eosinophils and a lower FEV_1/FVC ratio, indicating airway

obstruction, than obese patients without the metabolic syndrome. Blood eosinophils (%) in morbidly obese subjects were related to FEV_1/FVC, whereas monocytes were not. After adjustment for multiple variables, the relationship between FEV_1/FVC ratio and eosinophils remained intact. Although the differences are small, it strengthens our hy-

Table 4 Univariate linear regression analysis of FEV_1/FVC

	Regression coefficient	Standard Error	p Value[2]
Monocytes (%)	-0.079	0.162	0.626
Eosinophils (%)	-0.806	0.290	0.006
CRP (mg/mL)	0.075	0.045	0.098
Abdominal circumference (cm)	-0.058	0.021	0.006
Body mass index (kg/m^2)	0.041	0.047	0.387
OSAS (Eppworth Sleepiness Scale)[1]	0.311	0.141	0.029
GERD (GERD questionnaire)	0.068	0.157	0.667

[1] Missing values n=148

[2] Data presented as linear regression coefficient, p-value for simple linear regression analysis

GERD, Gastro Esophageal Reflux Disease; OSAS, Obstructive Sleep Apnea Syndrome

Table 5 Univariate regression analysis of relation of components of metabolic syndrome and FEV_1/FVC ratio

	Regression coefficient	Standard error	p Value[1]
Abdominal circumference	NA		
Hypertriglycemia	-1.119	0.739	0.130
Low serum HDL- cholesterol	0.712	0.686	0.300
Hypertension	-1.612	0.774	0.038
High serum glucose	-0.010	0.753	0.989

[1] Data presented as linear regression coefficient, p-value for linear regression analysis

Abdominal circumference is not applicable, because all patients fulfill the criteria for abdominal circumference according to the NCEP-ATP III criteria for metabolic syndrome

Table 6 Multiple regression analysis FEV_1/FVC ratio

	Whole group (n=408) (Adj R^2 = 0.074)		
	Regression coefficient	**95% CI**	**p-Value**
Eosinophils (%)	-0.113	-1.247- -0.118	0.018
Use of inhalationcorticosteroids	-0.025	-3.635-2.122	0.606
Pack years	-0.259	-0.162- -0.076	<0.001

Variables associated with FEV_1/FVC ratio in univariate analysis at a p-value of <0.1 were examined in the multiple linear regression analysis. Since the FEV_1/FVC ratio as percentage predicted is already corrected for height, age and gender we did not add this variables to the model. As eosinophils and abdominal circumference are correlated, we selected only one variable to prevent co-linearity. We omitted OSAS because of the large proportion of missing data.

pothesis that the presence of the metabolic syndrome could play a role in lung function impairment, through the induction of systemic inflammation, in particular mediated by blood eosinophils. Whether this also leads to asthma on the long term still remains to be elucidated.

To our knowledge this is the first study concerning lung function and the metabolic syndrome in a cohort of only morbidly obese subjects. Secondly, comorbid conditions associated with obesity such as OSAS and GERD were taken into account in the current study. Thirdly, adiposity was not only assessed with BMI, but also with abdominal circumference. Although one would expect that all our subjects have the metabolic syndrome, we found a 65% prevalence of the metabolic syndrome in our group, which corresponds with 60% of the morbidly obese in the NHANES III cohort[16].

Various studies have shown that obesity causes a modest reduction in total lung capacity (TLC), and a larger reduction in functional residual capacity (FRC)[17]. However, we were unable to perform a TLC measurement in all subjects to rule out a restrictive pattern. The FEV_1/FVC ratio is usually well preserved in obese subjects, or even increased. This could explain the high mean FEV_1/FVC ratio in our subjects, and therefore we have used the FEV_1/FVC ratio as a continuous variable and did not use a cutoff value of 70% predicted. Furthermore, in contrast to the FEV_1/FVC, the FEV_1 is influenced by BMI, hence our focus on the FEV_1/FVC ratio.

The prevalence of self-reported asthma was similar in the two groups. We did not perform methacholine-provocation tests, so a definitive diagnosis of asthma was often not possible. Since misdiagnosis of asthma is a relevant issue, also in the obese[18], we felt more comfortable using objective parameters instead of a presumed diagnosis.

Since the metabolic syndrome was associated with the FEV_1/FVC ratio in univariate analysis, we investigated which of the components of the metabolic syndrome contributed to this relationship. Hypertension was the only component that was significantly associated with a reduced FEV_1/FVC ratio after multiple backward regression analysis. Hypertension may have the strongest association with systemic inflammation, as proposed by Irace *et al.*[19]. We could also confirm the results of Leone *et al.*[10] showing that there is indeed a relationship between abdominal circumference (in cm) and the FEV_1/FVC ratio. Interestingly we found a correlation between blood eosinophil percentage and abdominal circumference, were we found no correlation between blood eosinophil percentage and BMI, indicating that it is mainly the place of the fat that matters. This suggests that the increased abdominal circumference of subjects with the metabolic syndrome causes the relative eosinophilia.

Obesity is a state of chronic low grade systemic inflammation. Leukocyte count is considered a marker of systemic inflammation. Several epidemiological studies have already noted a relationship between some components of metabolic syndrome and leukocytes[20, 21]. Several studies showed an increased eosinophil percentage in obe-

sity[22] or in the metabolic syndrome[20, 21]. C-reactive protein (CRP) is a traditional marker of inflammation, and is well correlated with BMI[23]. Even though our study found no difference in CRP between the two groups - we did not use high-sensitivity CRP measurements - monocyte and eosinophils percentage in the blood were higher in those with the metabolic syndrome. Our study suggests that increased numbers or circulating eosinophils could be a specific manifestation of the systemic inflammation associated with the metabolic syndrome.

The question remains why there is relative eosinophilia in the obese. Traditionally, eosinophils are related to allergic diseases, asthma and parasitic infections. The fat tissue is a source of adipokines, which are considered to play a role in the low-grade systemic inflammation in obesity[24]. Leptin –mainly produced by adipose tissue- is a pro-inflammatory agent. Serum leptin is markedly increased in obese humans, correlating to BMI[25], it activates eosinophils[26] and increases their survival[27]. Serum leptin levels are elevated in adults of normal weight with impaired lung function[28]. Eotaxin, is an eosinophil-specific chemokine that is increased in obesity[29]. Adipocytes produce more eotaxin when stimulated by leptin[30]. Plasma adiponectin - an anti-inflammatory hormone - is reversely correlated to BMI[31]. The leptin/adiponectin ratio is a marker of insulin resistance[32] and the metabolic syndrome[33]. Thus, both leptin and possibly eotaxin could contribute to relative eosinophilia in the obese. Unfortunately, we do not have data on leptin, adiponectine and eotaxin to further support their role in the observed eosinophilia.

Another question is whether this relative eosinophilia in the peripheral blood also has local effects on the bronchial tissue, and causes or enhances the bronchial inflammation as seen in asthma. Asthma-like symptoms are common in patients with the metabolic syndrome, and their pulmonary function is impaired[34, 35]. Although we did find differences in pulmonary function between subjects with and without the metabolic syndrome, there was no difference in prevalence of self-reported asthma between the two groups. This is however unreliable in the morbidly obese[18]. The characteristics of airway inflammation in asthma (exhaled nitric oxide (eNO) and inflammatory cells in induced sputum) have been investigated in obesity and are still subject to debate. De Winter – de Groot *et al.* showed that a higher BMI was associated with a higher eNO in healthy patients[36]. Several studies have found no –or even an inverse– relationship between the number of sputum eosinophils and BMI[37]. We found no difference in eNO between subjects with and without the metabolic syndrome. Induced sputum or bronchial biopsies could have helped to solve this question, but were unfeasible in this study. Since there was no difference in the use of inhaled corticosteroids, this could not have influenced our results of eNO.

Our study includes several limitations. We did not measure TLC values, so we were not able to firmly assess a restrictive lung function pattern. Also, we did not perform

methacholine-provocation tests, so a definite diagnosis of asthma was often not possible. The FEV_1/FVC ratio however, is easy to measure and widely used in clinical practice. Although the differences in FEV_1/FVC and eosinophils between subjects with and without the metabolic syndrome were small, the difference was significant despite the fact that our study groups consisted of unselected subjects. There probably is a selection-bias since we only included patients who were willing to undergo bariatric surgery. It is widely known that most of the subjects who undergo bariatric surgery are female. This explains the female predominance among our subjects. Furthermore, we did not measure adipocytokines or high sensitivity-CRP. We did not include a non-obese control group as comparison for low grade inflammation, and we cannot fully exclude that smoking might have contributed to a state of low-grade inflammation. However, we corrected for smoking in the multiple regression analysis. Finally, we realize that a cross-sectional association between metabolic syndrome and lung function cannot establish causality. However, Naveed *et al.*[12] have recently shown that the metabolic syndrome predicts a steeper FEV_1 decline over time, suggesting that the systemic inflammation produced by metabolic syndrome may impact the progression to abnormal lung function in a longitudinally followed cohort.

In summary, our study shows that there is a small, but statistical significant, difference in eosinophils and FEV_1/FVC between subjects with and without the metabolic syndrome. After correction for other variables, an association between blood eosinophils and FEV_1/FVC remained. Although the differences we have found were relatively small, it might support our hypothesis that the presence of the metabolic syndrome may influence lung function impairment, through the induction of systemic inflammation, in particular mediated by blood eosinophils. Further research with a firm diagnosis of asthma and assessment of peripheral airway inflammation is necessary. Moreover, in order to establish causality between the metabolic syndrome and lung function impairment, longitudinal studies in morbidly obese patients before and after bariatric surgery are needed.

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REFERENCES

1. Organisation WH. Obesity and overweight Fact Sheet no 311. 2011 [cited; Available from: http://www.who.int/mediacentre/factsheets/fs311/en/index.html
2. Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005;115(5):897-909.
3. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *Bmj* 2000;320(7238):827-32.
4. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109(3):433-8.
5. Selby JV, Friedman GD, Quesenberry CP, Jr. Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. *Am J Epidemiol* 1990; 131(6):1017-27.
6. Ford ES, Mannino DM. Prospective association between lung function and the incidence of diabetes: findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Diabetes Care* 2004;27(12):2966-70.
7. Yeh HC, Punjabi NM, Wang NY, Pankow JS, Duncan BB, Cox CE, Selvin E, Brancati FL. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* 2008;31(4):741-6.
8. Cirillo DJ, Agrawal Y, Cassano PA. Lipids and pulmonary function in the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2002;155(9):842-8.
9. Bottai M, Pistelli F, Di Pede F, Carrozzi L, Baldacci S, Matteelli G, Scognamiglio A, Viegi G. Longitudinal changes of body mass index, spirometry and diffusion in a general population. *Eur Respir J* 2002;20(3):665-73.
10. Leone N, Courbon D, Thomas F, Bean K, Jego B, Leynaert B, Guize L, Zureik M. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med* 2009;179(6):509-16.
11. Lin WY, Yao CA, Wang HC, Huang KC. Impaired lung function is associated with obesity and metabolic syndrome in adults. *Obesity* 2006;14(9):1654-61.
12. Naveed B, Weiden MD, Kwon S, Gracely EJ, Comfort AL, Ferrier N, Kasturiarachchi KJ, Cohen HW, Aldrich TK, Rom WN, Kelly K, Prezant DJ, Nolan A. Metabolic syndrome biomarkers predict lung function impairment: a nested case-control study. *Am J Respir Crit Care Med* 2012;185(4):392-9.
13. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540-5.
14. Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, Lind T. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 2009;30(10):1030-8.
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005;26(2):319-38.
16. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med* 2003;163(4):427-36.
17. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med* 2006;174(2): 112-9.

18. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Doucette S, Fergusson D. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179(11):1121-31.
19. Irace C, Cortese C, Fiaschi E, Carallo C, Sesti G, Farinaro E, Gnasso A. Components of the metabolic syndrome and carotid atherosclerosis: role of elevated blood pressure. *Hypertension* 2005;45(4): 597-601.
20. Kim DJ, Noh JH, Lee BW, Choi YH, Chung JH, Min YK, Lee MS, Lee MK, Kim KW. The associations of total and differential white blood cell counts with obesity, hypertension, dyslipidemia and glucose intolerance in a Korean population. *J Korean Med Sci* 2008;23(2):193-8.
21. Shim WS, Kim HJ, Kang ES, Ahn CW, Lim SK, Lee HC, Cha BS. The association of total and differential white blood cell count with metabolic syndrome in type 2 diabetic patients. *Diabetes Res Clin Pract* 2006;73(3):284-91.
22. Cottam DR, Schaefer PA, Shaftan GW, Velcu L, Angus LD. Effect of surgically-induced weight loss on leukocyte indicators of chronic inflammation in morbid obesity. *Obes Surg* 2002;12(3):335-42.
23. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *Jama* 1999;282(22):2131-5.
24. Ronti T, Lupattelli G, Mannarino E. The endocrine function of adipose tissue: an update. *Clin Endocrinol (Oxf)* 2006;64(4):355-65.
25. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;334(5):292-5.
26. Kato H, Ueki S, Kamada R, Kihara J, Yamauchi Y, Suzuki T, Takeda M, Itoga M, Chihara M, Ito W, Kayaba H, Chihara J. Leptin has a priming effect on eotaxin-induced human eosinophil chemotaxis. *Int Arch Allergy Immunol* 2011;155(4):335-44.
27. Conus S, Bruno A, Simon HU. Leptin is an eosinophil survival factor. *J Allergy Clin Immunol* 2005; 116(6):1228-34.
28. Sin DD, Man SF. Impaired lung function and serum leptin in men and women with normal body weight: a population based study. *Thorax* 2003;58(8):695-8.
29. Vasudevan AR, Wu H, Xydakis AM, Jones PH, Smith EO, Sweeney JF, Corry DB, Ballantyne CM. Eotaxin and obesity. *J Clin Endocrinol Metab* 2006;91(1):256-61.
30. Kim HJ, Kim CH, Lee DH, Han MW, Kim MY, Ju JH, Do MS. Expression of eotaxin in 3T3-L1 adipocytes and the effects of weight loss in high-fat diet induced obese mice. *Nutr Res Pract* 2011;5(1): 11-9.
31. Engeli S, Feldpausch M, Gorzelniak K, Hartwig F, Heintze U, Janke J, Mohlig M, Pfeiffer AF, Luft FC, Sharma AM. Association between adiponectin and mediators of inflammation in obese women. *Diabetes* 2003;52(4):942-7.
32. Finucane FM, Luan J, Wareham NJ, Sharp SJ, O'Rahilly S, Balkau B, Flyvbjerg A, Walker M, Hojlund K, Nolan JJ, Savage DB. Correlation of the leptin:adiponectin ratio with measures of insulin resistance in non-diabetic individuals. *Diabetologia* 2009;52(11):2345-9.
33. Yoon JH, Park JK, Oh SS, Lee KH, Kim SK, Cho IJ, Kim JK, Kang HT, Ahn SG, Lee JW, Lee SH, Eom A, Kim JY, Ahn SV, Koh SB. The ratio of serum leptin to adiponectin provides adjunctive information to the risk of metabolic syndrome beyond the homeostasis model assessment insulin resistance: The Korean Genomic Rural Cohort Study. *Clin Chim Acta* 2011;412(23-24):2199-205.
34. Lee EJ, In KH, Ha ES, Lee KJ, Hur GY, Kang EH, Jung KH, Lee SY, Kim JH, Lee SY, Shin C, Shim JJ, Kang KH, Yoo SH. Asthma-like symptoms are increased in the metabolic syndrome. *J Asthma* 2009; 46(4):339-42.

35. Thuesen BH, Husemoen LL, Hersoug LG, Pisinger C, Linneberg A. Insulin resistance as a predictor of incident asthma-like symptoms in adults. *Clin Exp Allergy* 2009;39(5):700-7.
36. De Winter-de Groot KM, Van der Ent CK, Prins I, Tersmette JM, Uiterwaal CS. Exhaled nitric oxide: the missing link between asthma and obesity? *J Allergy Clin Immunol* 2005;115(2):419-20.
37. Sutherland TJ, Cowan JO, Young S, Goulding A, Grant AM, Williamson A, Brassett K, Herbison GP, Taylor DR. The association between obesity and asthma: interactions between systemic and airway inflammation. *Am J Respir Crit Care Med* 2008;178(5):469-75.

5

Bronchial and systemic inflammation in morbidly obese asthmatic subjects: a biopsy study

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To the editor

Asthma in the obese has been described as a specific phenotype, with a late onset and high symptom expression[1]. However, the nature of bronchial inflammation in obese subjects with asthma is not fully understood. In contrast to eosinophilic airway inflammation in lean asthmatics, a predominance of airway neutrophilia has been reported in obese asthmatic women[2]. Some groups reported increased sputum neutrophil counts[2, 3], whereas others found no increase of neutrophilic inflammation in obese asthma patients[4, 5].

All aforementioned studies in obese asthmatics investigated induced sputum or brush biopsies[6] which may not fully reflect tissue inflammation. Thus far, only one study has described the analysis of bronchial biopsies in obese asthmatics, showing increased eosinophil counts in patients with severe asthma and obesity as compared to lean asthmatics[7]. However, that study did not include an obese control group, nor were other cell populations investigated such as airway neutrophils. To our knowledge, there are no data on bronchial biopsies from morbidly obese patients with mild-to-moderate asthma compared to morbidly obese control subjects without asthma.

We performed a cross-sectional study in 27 morbidly obese patients with asthma, defined according to GINA guidelines[8] and 43 morbidly obese control subjects undergoing bariatric surgery. Some of the results of this study have been previously reported in the form of an abstract[9].

This study is part of a larger study, the results of which have been reported elsewhere[10]. Subjects were between 18 and 50 years of age, with a BMI above 35 kg/m^2, and were excluded if they smoked more than 10 cigarettes per day or had smoked more than 10 pack years. The study was approved by the local ethics committee (Netherlands Trial Register 3204), and all subjects gave written informed consent. Lung function tests, asthma control, asthma quality of life, comorbidities, parameters of systemic inflammation and cell counts of bronchial biopsies were compared between obese patients with asthma and obese control patients.

A total of 86 patients were included[10], of whom 70 patients (table 1) had bronchial biopsies with acceptable quality for further analysis. When comparing the obese patients with asthma and obese control groups, no differences were detectable in several parameters assessed in peripheral blood, except for the neutrophil count and levels of serum IL-6 which were both slightly, but significantly, increased in the morbidly obese asthma group compared to the morbidly obese control group (table 1). We found no other significant differences between these groups concerning markers of systemic inflammation (IL-8, hs-CRP, TNFα, GM-CSF, leptin or adiponectin).

When assessing bronchial biopsies, there were no significant differences in submucosal cell counts of eosinophils, neutrophils, mast cells, macrophages, B-cells, CD4$^+$ or CD3$^+$ T-cells (figure 1 A – G). CD8$^+$ T-cells were significantly lower in the asthma group

Table 1 Demographics of the study population

	Asthma N= 27	**No asthma** N=43	**p Value**
Gender (%female)	77.8%	81.4%	0.764
Ethnicity (%non-Caucasian)	18.5%	11.6%	0.493
Age (years)	33 (19-48)	38 (19-50)	0.623
Weight (kg)	127.1 (101-202)	126.0 (94-199)	0.850
Body Mass index (kg/m^2)	44.59 (38.4-63.8)	43.35 (36.9-60.0)	0.326
Abdominal circumference (cm)	130 (112-165)	128 (98-200)	0.985
Bio-impedance			
Fat free Mass	58.2 (50.1-100.5)	62.3 (48.0-83.9)	0.248
Fat weight (%)	50.9 (37.6-70.4)	51.1 (31.1-59.7)	0.878
Fat weight (kg)	65.4 (44.5-134.4)	63.0 (33.9-100)	0.396
Smoking status			0.058
% never smoked	55.6%	72.1%	
% stopped smoking	14.8%	18.6%	
% current smoker	29.6%	9.3%	
Pack years	0 (0-10)	0 (0-10)	0.246
Asthma			
Asthma Control Questionnaire[1]	1.1 (0.4-2.9)	0.3 (0-2.9)	0.001
Asthma Quality of Life Questionnaire [2]	5.8 (3.7-6.8)	6.6 (3.7-7.0)	0.007
Medication use at inclusion study			
Short acting bronchodilator	48.1%	23.3%	0.039
Long acting bronchodilator	3.7%	2.3%	1.000
Antileukotrienes	0%	2.3%	1.000
B_2 sympaticomimetica/ ICS	22.2%	7.0%	0.070
Inhaled corticosteroids	22.2%	7.0%	0.079
Antihistamines	25.9%	11.6%	0.192
Nasal corticosteroids	14.8%	11.6%	0.726
Atopy			
Atopy [3]	70.4%	41.9%	0.027
IgE (kU/L) **	205 (5-1838)	59 (1.4-761)	0.049
Comorbidities			
Epworth Sleepiness Scale	2 (0-8)	2 (0-15)	0.670
GERD-questionnaire	6 (4-12)	7 (2-14)	0.524
Steps a day	5107 (2156-12176)	5158 (2061-11705)	0.766
Metabolic syndrome	51.9%	51.2%	1.000
Lung function			
Spirometry			
FEV_1, pre(% predicted)	88 (66-119)	97 (73-125)	0.023
FEV_1, post (% predicted)	95 (74-118)	101 (75-129)	0.141
FVC, pre (% predicted)	97 (75-126)	102 (79-144)	0.623
FEV1/FVC, pre (%)	76 (63-86)	81 (66-93)	0.010
RV, post (% predicted) *	68 (39-126)	75 (33-118)	0.757
ERV, post (% predicted) *	45 (24-78)	47 (11-66)	0.682
TLC, post (% predicted) *	95 (80-106)	94 (76-114)	0.822
FRC, post (% predicted) *	60 (47-95)	61 (41-88)	0.925

Table 1 Demographics of the study population (continued)

	Asthma N= 27	**No asthma** N=43	**p Value**
RV/TLC, post (%) *	22 (10-41)	25 (12-86)	0.249
Reversibility FEV_1	10 (-6-20)	3 (-7-11)	0.001
Fe_{NO} (ppb) **	16 (5-45)	16 (7-53)	0.934
Diffusion capacity (% predicted)	95 (69-130)	96 (69-134	1.000
PD_{20} (mg)	0.33 (0.04-1.8)	> 1.8	
IOS			
R_5 (kPa/sec)	0.70 (0.42-1.39)	0.56 (0.32-0.85)	0.003
R_{20} (kPa/sec)	0.45 (0.27-1.03)	0.42 (0.19-0.68)	0.623
R_5-R_{20}	0.26 (0.06-0.66)	0.15 (0.03-0.28)	<0.001
X_5 (kPa/sec)	-0.26 (-0.87- -0.12)	-0.20 (-0.41- -0.08)	0.061
F_{res} (Hz)	22.67 (10.5-29.0)	17.95 (8.4-23.2)	<0.001
Laboratory[4]			
Cholesterol (mmol/L)	4.7 (3.4-7.4)	5.0 (2.3-6.9)	0.972
HDL-cholesterol (mmol/L)	1.1 (0.7-2.3)	1.1 (0.7-2.1)	0.910
LDL-cholesterol (mmol/L)	2.9 (1.6-5.1)	3.0 (0.7-4.8)	0.920
Triglyceride (mmol/L)	1.7 (0.6-3.3)	1.4 (0.4-5.1)	0.326
Glucose (mmol/L)	5.6 (4.6-9.5)	5.6 (4.0-27.1)	0.910
Vitamin D (nmol/L)	40.5 (11-127)	40.0 (10-62)	0.877
Peripheral blood count			
Leukocytes (10^9 /L)	8.7 (5.3-13.1)	7.2 (5.2-11.9)	0.141
Neutrophils (%)	61 (45-72)	59 (46-70)	0.049
Lymphocytes (%)	28 (17-45)	32 (20-47)	0.141
Monocytes (%)	0.5 (0.4-1.5)	0.5 (0.3-0.9)	0.141
Eosinophils (%)	2 (0-6)	2 (0-8)	0.942
Basophils (%)	0 (0-1)	0 (0-2)	0.850
HS-CRP (pg/ml)	36.0 (4.3-142.0)	31.5 (3.7-120.4)	0.732
IL-6 (pg/ml)	0.72 (0.61-3.78)	0.70 (0.7-13.3)	0.020
IL-8 (pg/ml)	3.86 (1.79-13.46)	3.84 (1.86-9.12)	0.877
TNF-alfa (pg/ml)	0.8 (0.8-1.3)	0.8 (0.8-1.0)	0.910
GM-CSF (pg/ml)	0.61 (0.61-3.78)	0.61 (0.61-8.44)	0.275
Leptin (ng/ml)	68 (18-100)	70 (11-100)	0.877
Adiponectin (pg/ml)	12.0 (4.5-22.0)	14.1 (0.06-28.9)	0.251

Data are presented as median (min-max)

* Because of weight limitations (<150 kg) of body box different numbers; asthma = 18, control = 30

** Log transformed for statistical purposes

[1] Scores of the asthma control questionnaire range from 0 to 6, with lower scores indicating better asthma control

[2] Scores of the AQLQ range from 1 to 7, with higher scores indicating better asthma-specific quality of life

[3] Defined as either one positive reaction to the skin-prick test or one positive reaction to specific IgE inhalation screen

[4] Non-fasting blood sample

Diffusion capacity, kCO; ERV, expiratory reserve volume; Fe_{NO}, exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; ICS, inhaled corticosteroid; PD_{20}, provocative dose of methacholine inducing a 20% fall in FEV_1; RV, residual volume; TLC, total lung capacity

compared to the controls (median 682 versus 1017, p=0.014; figure 1H). There was no difference in CD4/CD8 ratio or in reticular basement membrane (RBM) thickness between the two groups (figure 1I-J).

In contrast, a subgroup analysis showed that asthmatics with uncontrolled asthma (Asthma Control Questionnaire score >1.5) compared to obese control had significantly higher levels of IL-6 (median 0.89 vs. 0.70 pg/ml, p<0.001) and lower adiponectin (median 9.2 vs. 14.1 ng/ml, p=0.014), whereas we found no differences in cell counts in bronchial biopsies. Further subgroup analysis (ICS use at time of biopsy, females, high IgE, large abdominal circumference, childhood-onset versus adult onset asthma, smoking) showed no differences between obese control patients and obese patients with asthma regarding all parameters representing bronchial or systemic inflammation.

We found no significant correlations between clinical parameters (lung function parameters [FEV_1, FEV_1/FVC, provocative dose of methacholine inducing a 20% fall in FEV_1, and fractional exhaled nitric oxide] or symptoms (Asthma Control Questionnaire or Asthma Quality of Life Questionnaire) and bronchial or systemic inflammation.

In contrast to previous reports[2, 7], the present results show neither eosinophilic nor neutrophilic inflammation in the group of morbidly obese asthmatics. In contrast to Desai and colleagues[7], who analyzed exclusively patients with severe asthma, we included only patients with mild-to-moderate asthma. Furthermore, the median body mass index was significantly higher in our study (44 kg/m^2) compared to Desai's study (36 kg/m^2).

In addition, we also investigated other cell types in the bronchial submucosa, such as mast cells, macrophages, B-cells, $CD3^+$, and $CD4^+$ and positive T-cells, and again found no differences between the asthma and the control group. Moreover, we also measured the reticular basement membrane thickness, as a marker of airway remodeling[11], and found no difference between obese asthmatics and obese control patients. These data suggest that asthma in this cohort is not driven by a classical Th2-mediated mechanism and probably needs to be regarded as a distinct phenotype of the disease that is not related to significant inflammatory responses in the airways. It needs to be noted that we did not assess innate immune cells such as innate lymphoid cells, natural killer cells and dendritic cells in our analysis, and therefore cannot exclude the possibility that differences existed in these cells between the asthma and control groups.

Sutherland and colleagues[12] previously demonstrated that asthma phenotypes are not homogenous in obese individuals. However, in the present study, we found no differences in lung function, symptoms, or inflammation parameters when analyzing different subgroups such as subjects with a larger abdominal circumference, age of onset of asthma, high IgE or use of inhaled corticosteroids. We cannot exclude the possibility that morbidly obese mild to moderate asthma patients constitute an obese asthma phenotype that is characterized by the absence of bronchial inflammation.

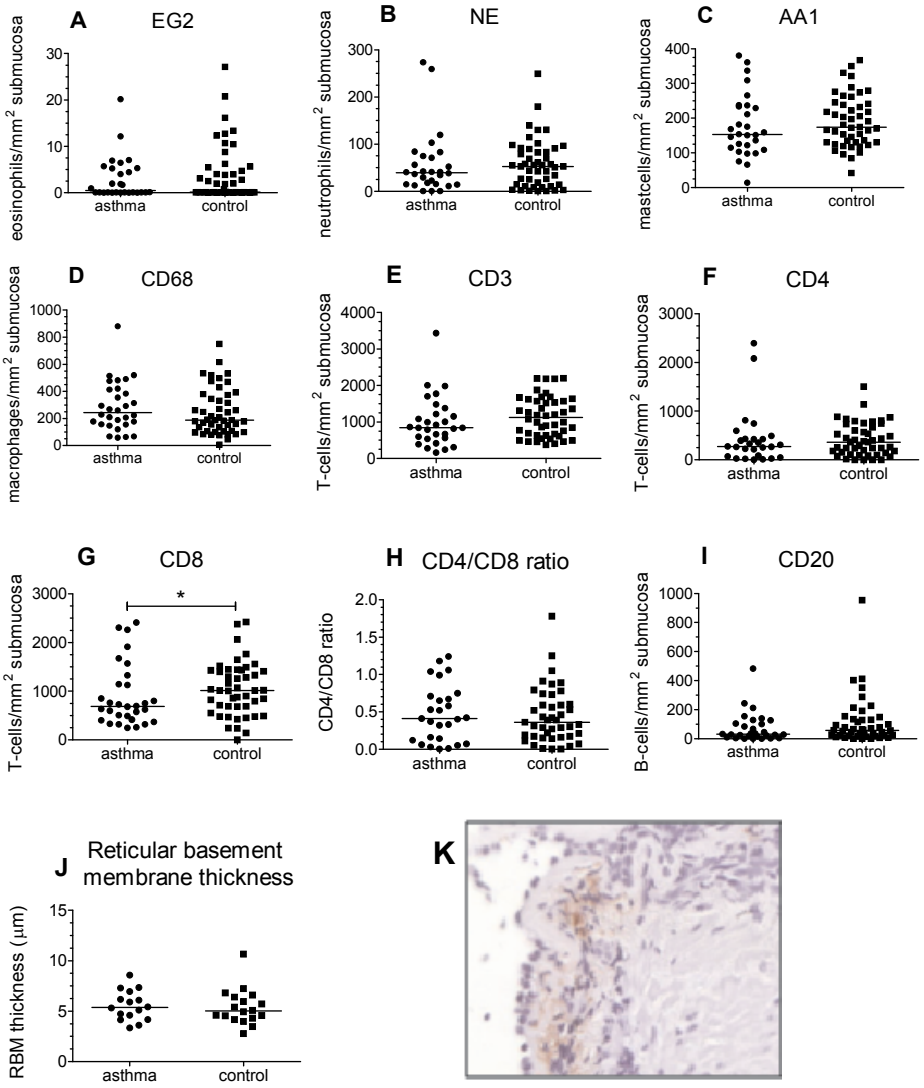

Figure 1 Bronchial submucosal cell counts and reticular basement membrane thickness

Bronchial submucosal cell count in obese subjects with and without asthma (a) eosinophils (p=1.000) (asthma n=27, control n=43), (b) neutrophils (p=0.141), (c) mast cells, (d) macrophages (p=0.326), (e) B-cells (p=0.141), (f) $CD4^+$ T cells (p=1.000), (g) $CD3^+$ T cells (p=0.326), (h) $CD8^+$ T cells (p=0.014), (i) reticular basement membrane thickness (p=0.874) (asthma n=15, control n=18), (j) CD4 / CD8 ratio (k) Photomicrograph of a bronchial biopsy from an obese subject with asthma showing stained eosinophils.
The horizontal bar is the median.

Several hypotheses may explain the relationship between obesity and asthma, such as co-morbidities (Gastroesophageal reflux disease, obstructive sleep apnea syndrome) or the metabolic syndrome[13] for which we found no differences between obese patients with asthma and obese control patients. Body composition in the obese, however, might cause asthmatic symptoms and lung function impairment[14], and in particular, the significant difference in impulse oscillometry (R_5-R_{20}) suggests an abnormality in the lung periphery, which is in line with recently reported data[15].

The strength of our study is the inclusion of an obese control group of subjects without asthma. Furthermore, the diagnosis of asthma was performed strictly according to the Global Initiative for Asthma guidelines, and was not based on a doctor diagnosis in which symptoms play a major role, which has been shown to be incorrect[16]. Nonetheless, there are some limitations to our study. First, we did not include a lean asthma or lean control group. Furthermore, we used a heterogeneous asthma group with a majority of subjects with mild to moderate disease and relatively few symptoms, in contrast to other studies that investigated more severe obese patients with asthma.

In summary, despite evidence for systemic inflammation, which seemed to be related to the level of asthma control, there was no evidence for bronchial inflammation, characterized by increased numbers of eosinophils or neutrophils. Further research aiming at the effects of weight reduction on inflammation, symptoms, lung function and quality of life in the morbidly obese may provide valuable further insights in the pathogenesis and treatment of asthma in that population.

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REFERENCES

1. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178(3):218-24.
2. Scott HA, Gibson PG, Garg ML, Wood LG. Airway Inflammation is Augmented by Obesity and Fatty Acids in Asthma. *Eur Respir J* 2011;38(3):594-602.
3. Telenga ED, Tideman SW, Kerstjens HA, Hacken NH, Timens W, Postma DS, van den Berge M. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. *Allergy* 2012;67(8):1060-8.
4. Sutherland TJ, Cowan JO, Young S, Goulding A, Grant AM, Williamson A, Brassett K, Herbison GP, Taylor DR. The association between obesity and asthma: interactions between systemic and airway inflammation. *Am J Respir Crit Care Med* 2008;178(5):469-75.
5. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? *Chest* 2008; 134(2):317-23.
6. Sideleva O, Suratt BT, Black KE, Tharp WG, Pratley RE, Forgione P, Dienz O, Irvin CG, Dixon AE. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. *Am J Respir Crit Care Med* 2012;186(7):598-605.
7. Desai D, Newby C, Symon FA, Haldar P, Shah S, Gupta S, Bafadhel M, Singapuri A, Siddiqui S, Woods J, Herath A, Anderson IK, Bradding P, Green R, Kulkarni N, Pavord I, Marshall RP, Sousa AR, May RD, Wardlaw AJ, Brightling CE. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. *Am J Respir Crit Care Med* 2013;188(6):657-63.
8. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31(1):143-78.
9. van Huisstede A, van Rijn VE, Rudolphus A, Castro Cabezas M, Mannaerts GM, Taube C, Hiemstra PS, Braunstahl GJ. Bronchial and systemic inflammation in morbidly obese asthmatic subjects: a biopsy study. In: ATS 2014. San Diego; 2014.
10. van Huisstede A, Castro Cabezas M, van de Geijn GJ, Mannaerts GH, Njo TL, Taube C, Hiemstra PS, Braunstahl GJ. Underdiagnosis and overdiagnosis of asthma in the morbidly obese. *Respir Med* 2013;107(9):1356-64.
11. Bourdin A, Neveu D, Vachier I, Paganin F, Godard P, Chanez P. Specificity of basement membrane thickening in severe asthma. *J Allergy Clin Immunol* 2007;119(6):1367-74.
12. Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, Stream AR, Fahy JV. Cluster analysis of obesity and asthma phenotypes. *PLoS One* 2012;7(5):e36631.
13. Brumpton BM, Camargo CA, Jr., Romundstad PR, Langhammer A, Chen Y, Mai XM. Metabolic syndrome and incidence of asthma in adults: the HUNT study. *Eur Respir J* 2013;42(6):1495-502.
14. Brumpton B, Langhammer A, Romundstad P, Chen Y, Mai XM. General and abdominal obesity and incident asthma in adults: the HUNT study. *Eur Respir J* 2013;41(2):323-9.
15. Al-Alwan A, Bates JH, Chapman DG, Kaminsky DA, DeSarno MJ, Irvin CG, Dixon AE. The nonallergic asthma of obesity. A matter of distal lung compliance. *Am J Respir Crit Care Med* 2014;189(12): 1494-502.
16. Scott S, Currie J, Albert P, Calverley P, Wilding JP. Risk of mis-diagnosis, Health related Quality of Life and Body Mass Index in Overweight Patients with doctor diagnosed asthma. *Chest* 2012; 141(3):616-24.

PART C

BARIATRIC SURGERY

6

Pulmonary function testing and complications of laparoscopic bariatric surgery

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ABSTRACT

Background: Obesity is associated with respiratory symptoms and impaired pulmonary function, which could increase the risk of complications after bariatric surgery.

Aim: To assess the relationship between pulmonary function parameters before, and the risk of complications after, laparoscopic bariatric surgery.

Methods: This prospective study included patients (age 18-60, BMI >35 kg/m2), who were eligible for bariatric surgery. Spirometry was performed in all patients. Complications up to 30 days after bariatric surgery were recorded.

Results: 485 patients were included (304 laparoscopic sleeve gastrectomy, 181 laparoscopic gastric bypass). There were 53 complications (8 pulmonary, 27 surgical, 14 infectious, 4 other) in 50 patients (10%). There were 35 re-admissions (7.2%), and 17 re-laparoscopies (3.5%). Subjects with and without complications did not differ significantly with respect to demographics, weight, BMI, abdominal circumference or fat percentage. Subjects with complications had a significantly lower mean FEV_1 (mean 86.9% predicted) and FVC (95.6% predicted) compared to patients without complications (95.9% predicted, p=0.005, and 100.1% predicted, p=0.045, respectively). After adjustment for age, gender, BMI and smoking, abnormal spirometry value remained the single predictive covariable of postoperative complications; $FEV_1/FVC<70\%$ adj. OR 3.1 (95%CI 1.4-6.8, p=0.006) and $\Delta FEV_1 \geq 12\%$ adj. OR 2.9 (95%CI 1.3-6.6, p=0.010).

Conclusion: The risk of pulmonary complications after laparoscopic bariatric surgery is low. However, subjects with abnormal spirometry test results have a threefold risk of complications after laparoscopic bariatric surgery. Preoperative pulmonary function testing might be useful to predict the risk of complications of laparoscopic bariatric surgery.

INTRODUCTION

Obesity is becoming a world-wide epidemic. In 2008, the WHO estimated that one out of ten persons of the world's adult population was obese[1]. Accordingly, the number of bariatric surgery procedures being performed is increasing every year, with a 22-fold increase between 1996 and 2008[2]. The postoperative morbidity rate after bariatric surgery is about 5%. Gupta showed in a large cohort study that postoperative pneumonia and respiratory failure, despite being infrequent complications of bariatric surgery, account for one fifth of the morbidity. Moreover, these complications are also associated with increased mortality[3] and represent largest attributable costs of all complications[4]. The prevention of complications of bariatric surgery is of great importance, especially since the operation is elective and complications are difficult to treat in this group of morbidly obese patients. Obesity is found to be a risk factor for the development of postoperative pulmonary complications after abdominal surgery[5]. Obesity-related co-morbidities may predispose obese patients to postoperative complications, as illustrated by the observation that asthma is 50% more prevalent among obese subjects[6] and obese asthma patients have worse asthma control[7], which might predispose them to postoperative complications.

Current guidelines do not indicate pulmonary function testing in patients without evidence of pre-existing lung disease who are evaluated for non-thoracic surgical procedures. It is, however, questionable whether this also holds true for the morbidly obese. Spirometry could identify patients who are at risk for complications, although this is not the current consensus[8]. Spirometry is mandatory in patients who are heavy smokers, or have complaints of dyspnea or cough[9]. However, there is a poor correlation between lung function measurements and the presence of symptoms[10], also among the morbidly obese.

Hamoui has shown that pulmonary function parameters prior to open bariatric surgery are predictive for complications after bariatric surgery[11]. However, bariatric surgery has developed during the last decade into a laparoscopic procedure which is considered to be a safer treatment than open surgery[12]. Laparoscopic procedures are typically associated with less postoperative pain, decreased opioid use, and earlier mobilization when compared with open procedures[13]. However, the prognostic added value of pulmonary function testing before laparoscopic bariatric surgery is unknown.

Since laparoscopic procedures are now standard, and little is known about the value of pulmonary function tests before laparoscopic bariatric surgery, we performed a prospective study to compare the predictive relationship between lung function parameters before laparoscopic bariatric surgery and the postoperative 30 days risk of complications, taking co-morbidities, demographic, and anthropomorphic features into

account. We hypothesized that abnormal lung function test results before surgery could identify patients at risk for complications of bariatric surgery.

MATERIALS AND METHODS

Study population

The subjects included in this study were consecutive patients who underwent a pre-operative screening program for bariatric surgery in the Sint Franciscus Gasthuis in Rotterdam, The Netherlands, between October 2009 and November 2011. Eligibility criteria for bariatric surgery were: age between 18 and 60 years, body mass index (BMI) either ≥ 40 kg/m^2 or ≥ 35 kg/m^2 combined with the presence of comorbidity such as diabetes mellitus, hypertension or proven obstructive sleep apnea syndrome (OSAS). Prior to surgery, subjects underwent physical examinations that included routine assessment of anthropometry and pulmonary function. Height and weight were measured wearing light clothes and no shoes. Body mass index was calculated as weight (in kg) divided by height (in m squared). Abdominal circumference was measured directly to the body surface midway between the lower rib margin and the ileac crest. Fat free mass and fat weight (in kg and % body weight) were measured using electrical impedance analysis (Bodystat 1500, Bodystat Ltd, British Isles)[14]. The presence of comorbidities was defined as follows: diabetes mellitus, hypertension or hyperlipidemia all by the use of medication, the presence of the metabolic syndrome according to the NCEP-ATP-III criteria[15], the diagnosis of asthma and COPD after consultation with a pulmonologist and pulmonary function tests, as described below. The Epworth Sleepiness Scale[16] questionnaire was used to assess OSAS, and the GERD-Questionnaire[17] for gastro-esophageal reflux disease (GERD).

All participating subjects gave informed consent. The local ethics committee (Toetsingscommissie Wetenschappenlijk Onderzoek Rotterdam e.o, trial number NL25637.101.08) approved the study protocol (Netherlands Trial Register number NTR3204).

Pulmonary function tests

Spirometry was performed with Vmax spirometer (Vmax SensorMedics Viasys, type Encore 20/22/229/62 Encore, Cardinal Health, USA) before and after 400 µg of inhaled salbutamol, with subjects in a sitting position and nose clips in place according to the American Thoracic Society / European Respiratory Society statement[18]. All values obtained were related to height, age and gender and expressed as percentage of their predicted value (reference ERS 1993). The pulmonary function test results are shown as prebronchodilator values unless otherwise indicated. The degree of reversibility in FEV_1, which indicates a diagnosis of asthma is generally accepted as ≥12% and 200 ml

from the pre-bronchodilator value ($\Delta FEV_1 \geq 12\%$)[19]. Because many lung diseases may result in reduced FEV_1, a useful assessment of airflow limitation is the ratio of FEV_1 to FVC. The FEV_1/FVC ratio is normally greater than 70%. Total Lung Capacity could only be measured if subjects were <150 kg. Exhaled nitric oxide (Fe_{NO}) was measured with Niox mino (Aerocrine, Sweden) and expressed in parts per billion (ppb)[20].

Bariatric surgery

All operations were laparoscopic, either sleeve gastrectomy[21] or Roux-en Y gastric bypass. Routine anesthesia was applied with desflurane and remifentanil. Both procedures were performed with the patient in a semi-reclining position (anti-Trendelenburg position) with the legs in split upward position (French position). All patients routinely received prophylaxis against deep venous thrombosis with pneumatic compression stocking and subcutaneous low molecular weight heparin during two weeks. Perioperative antibiotics (cefazoline 2 gram) were also routinely given. Patients were normally discharged the second day after surgery.

Complications

The cumulative 30-days postoperative complications were obtained from the patient charts and divided into pulmonary, surgical, infectious or other by a surgeon and a pulmonologist. The reasons for either hospital readmission or the problem found at relaparoscopy were scored as complications, but readmission or relaparoscopy itself were not scored as separate complications.

Statistical analyses

Analysis was not restricted to pulmonary problems, but included all complications. Patients were divided into groups with and without complications. Unadjusted between-group comparisons were performed using Student's t test or the Chi-square test (or Fisher's Exact test, where appropriate) and the Mann Whitney U test for nonparametric comparisons. Multiple logistic regression analysis (entered) was used to assess the relationship between preoperative factors and the risk of postoperative complications adjusted for other co-variables. Baseline variables associated with complications in univariate analysis at a p-value of <0.1 were examined in the logistic regression analysis. Age, sex, BMI and smoking status were added to the regression analysis. Since FEV_1 and FVC are associated, we used three different regression models which all contained one of the pulmonary function parameters. All analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, Illinois, USA). A two-sided $p<0.05$ was considered a statistically significant result.

RESULTS

485 patients were included (mean BMI 45.4 kg/m^2, M:F 100:385). There were in total 53 complications in 50 patients (10.3%) after bariatric surgery (as specified in table 1). There were 35 re-admissions (7.2%), of which seven patients were found to have no complications. Relaparoscopy was performed in 16 cases, relaparotomy in one case (total 3.5%). All of these subjects were found to have a complication (9 hematoma, 1 spleen injury, 1 anastomosis leakage, 3 anastomosis stenosis, 2 small bowel injuries, 1 abscess). No deaths occurred.

Baseline characteristics did not differ between subjects with or without complications (table 2), especially not in BMI, abdominal circumference or fat mass. The superobese patients (BMI>50 kg/m^2, n=104) did not have more complications than the subjects with BMI <50 kg/m^2 (n=381) (10.6% versus 10.2%, p=0.92). There was no difference in pre-existing comorbidities, e.g. asthma, diabetes, reflux (assessed with GERD-Q) or sleep apnea syndrome (assessed with ESS). There were no differences either in opera-

Table 1 Postoperative complications

	Frequency
Pulmonary complications	8 (1.6%)
Pneumonia	5
Pulmonary embolism	1
Pneumothorax	1
Lung abscess	1
Surgical complications	27 (5.6%)
Hematoma (intra-abdominal)	10
Spleen injury	3
Anastomotic leak	2
Anastomotic stenosis	3
Requirement for blood transfusion	4
Small bowel injury	2
Abscess (deep)	1
Stenosis (endoscopic dilatation)	1
Hypovolemic shock	1
Infectious complications	14 (2.9%)
Urinary tract infection	4
Abdominal wall infection	8
Unknown	2
Other complications	4 (0.8%)
Dehydration	3
Intensive Care admission for hyperglycaemia	1

tion technique used (sleeve gastrectomy or gastric bypass) or in American Society of Anesthesiologists (ASA) scoring between groups with or without complications. There was a trend towards longer operation duration in subjects with complications, and the median length of hospital stay was significantly longer in subjects with complications (table 2).

Subjects with complications had a significantly lower FEV_1 compared to subjects without complications (table 3). Subjects with complications more often had airflow reversibility (increase in FEV_1 after bronchodilatation of at least 12%) and airway obstruction ($FEV_1/FVC < 70\%$ predicted), compared to subjects without complications. There was no difference in TLC or Fe_{NO} between subjects with or without complications.

Abnormal spirometry requiring an intervention by means of additional medication, increased medication dose or pre-operative steroid course occurred more often in subjects with complications (26%) than in subjects without complications (14%, p=0.026). Subjects with a medication advice did not have longer operation duration or length of hospital stay.

Table 2 Baseline characteristics of subjects

	Subjects without complications N=435	**Subjects with complications N=50**	**p Value**
Age (years)	41.6 ± 11.1	40.7 ± 10.8	0.603
Weight (kg)	131.0 ± 22.4	136.1 ± 28.5	0.229
Body Mass Index (kg/m^2)	45.3 ± 6.2	46.5 ± 6.6	0.196
Abdominal circumference (cm)	131.6 ± 14.9	133.1 ± 17.0	0.536
Bioimpedance			
Fat Free Mass (kg)	63.78 ± 11.2	66.4 ± 14.4	0.164
Fat (%)	50.5 ± 7.0	51.4 ± 6.9	0.425
Fat (kg)	66.9 ± 16.3	71.2 ± 18.9	0.117
Gender (% female)	79.5%	78.0%	0.799
Ethnicity (% Caucasian)	84.6%	86.0%	0.475
Smoking status			0.758
% Never	42%	46%	
% Former	33%	28%	
% Active	25%	26%	
Pack years *	2.2 (0-12.5)	2.2 (0-14)	0.754
Comorbidity			
Asthma	23.0%	28.0%	0.429
COPD	3.2%	2.0%	0.999
Diabetes mellitus	32.0%	33.3%	0.856

Table 2 Baseline characteristics of subjects (continued)

	Subjects without complications N=435	Subjects with complications N=50	p-Value
Hypertension	74.4%	68.8%	0.396
Hypercholesterolemia	35.8%	43.8%	0.281
Metabolic syndrome	64.6%	64.6%	0.993
Epworth Sleepiness Scale (OSAS) *	3 (2-4)	3 (1-4)	0.870
GERD-questionnaire	6.9 ± 2.3	6.4 ± 1.9	0.455
Surgery			
Operation (% sleeve gastrectomy)	63%	58%	0.470
Operation duration (minutes)	92.4 ± 40.4	102.9 ± 37.2	0.080
Admission (days)*	4 (3-4)	5 (4-7.25)	<0.001
ASA scoring			0.835
1 (%)	0.2%	0%	
2 (%)	36.8%	34.1%	
3 (%)	60.5%	61.4%	
4 (%)	2.4%	4.5%	

Unless stated otherwise, data presented as mean ± standard deviation or %

* Data presented as median (IQR)

ASA score, American Society of Anesthesiologists score; GERD, gastro-esophageal reflux disease; OSAS, obstructive sleep apnea syndrome

Table 3 Pulmonary function tests

	N	Subjects without complications	Subjects with complications	p Value
FEV_1 (% predicted)	485	92.9 ± 14.3	86.9 ± 13.5	0.005
FEV_1 < 80% predicted	485	17.1%	28.0%	0.057
FVC (% predicted)	485	100.1 ± 14.9	95.7 ± 13.0	0.045
FVC < 80% predicted	485	9.0%	10.0%	0.813
FEV_1/FVC (% predicted)	485	79.2 ± 5.9	77.7 ± 7.8	0.111
RV (% predicted, post)	212	76.9 ± 20.4	76.5 ± 14.3	0.941
FRC (% predicted, post)	212	66.0 ± 13.2	66.1 ± 12.3	0.993
TLC (% predicted, post)	212	94.8 ± 11.2	95.2 ± 8.4	0.889
Reversibility FEV_1 (%)	485	4.3 ± 4.9	5.5 ± 7.7	0.315
Fe_{NO} (ppb) *	225	14.5 (9.0-22.0)	17.0 (9.5-23.5)	0.676
$\Delta FEV_1 \geq 12\%$	485	7.2%	18.4%	0.007
FEV_1/FVC < 70% predicted	485	8.1%	20.0%	0.006

Unless stated otherwise, data presented as mean ± standard deviation or %

* Data presented as median (IQR)

Fe_{NO}, exhaled nitric oxide; FEV_1, Forced expiratory volume in one second; FRC, Functional Respiratory Capacity; FVC, Forced vital capacity; RV, Residual volume; TLC, Total Lung Capacity

Table 4 Multivariable logistic regression analysis of the risk of complications after laparoscopic bariatric surgery

	Model I			Model II			Model III		
	Exp (B)	**95% CI**	**p Value**	**Exp (B)**	**95% CI**	**p Value**	**Exp (B)**	**95% CI**	**p Value**
Age	0.992	0.966-1.019	0.558	0.990	0.964-1.017	0.466	0.992	0.965-1.019	0.548
Sex	0.903	0.443-1.843	0.780	1.045	0.504-2.171	0.905	0.892	0.434-1.832	0.755
BMI	1.028	0.982-1.076	0.238	1.032	0.986-1.081	0.176	1.018	0.970-1.068	0.469
Smoking status*	1.017	0.515-2.010	0.961	0.958	0.480-1.915	0.904	1.063	0.535-2.112	0.861
Constant	0.043		0.015	0.034		0.011	0.068		0.051
FEV_1 <80% predicted	1.865	0.953-3.652	0.069						
FEV_1/FVC <70% predicted				3.057	1.370-6.823	0.006			
$\Delta FEV_1 \geq 12\%$							2.933	1.298-6.629	0.010

* current smokers versus rest

All models consisted of the variables age, sex, BMI and smoking status. Since FEV_1 and FVC are associated, we used three different regression models which all contained one of the pulmonary function parameters. Model I added FEV_1 < 80% predicted as variable, model II added FEV_1/FVC <70% predicted as variable, and model III added $\Delta FEV_1 \geq 12\%$ as variable

FEV_1, Forced expiratory volume in one second; FVC, Forced vital capacity

Table 4 displays the results of three separate logistic regression analyses, after adjustment for age, sex, BMI and smoking status. Since FEV_1 and FVC are correlated, we used three different models which all contained one of the pulmonary function parameters. Airway reversibility ($\Delta FEV_1 \geq 12\%$) and airway obstruction ($FEV_1/FVC<70\%$) remained significant predictors of complications.

DISCUSSION

This study demonstrates that morbidly obese subjects with abnormal preoperative spirometric results, -- more specifically, airway obstruction ($FEV_1/FVC < 70\%$ predicted) (adj OR 3.1) or airflow reversibility (increase of $FEV_1 \geq 12\%$) (adj. OR 2.9) -- are more likely to develop postoperative complications after undergoing laparoscopic bariatric surgery.

To our knowledge, this is the first study which has investigated the association between preoperative pulmonary function testing and complications after laparoscopic bariatric surgery. Previous studies have investigated complications in open procedures[10] or both open and laparoscopic[22]. Furthermore, this study has also included sleeve gastrectomy, a rather new surgical technique as a standalone procedure. This study has used a large group of subjects, who were all well characterized.

The American Society for Metabolic and Bariatric Center of Excellence facilities report mentioned a 5% readmission rate and a 2% reoperation rate[23], which compares well with our rates (7% and 3.5% respectively). Also, our complication rate of 10% is comparable to other studies (3 to 24%). Surgical experience may have influenced the complication rates. Some studies suggest that leakage is more likely to occur when the surgeon is less experienced[24]. In the present study, procedures were performed by an experienced team in which each surgeon had carried out over 200 procedures. Furthermore, the highly standardized treatment protocol applied in our hospital, such as routine prophylaxis against deep venous thrombosis with pneumatic compression stocking and administration of subcutaneous heparin, probably also prevented complications.

There is considerable debate regarding the role of preoperative pulmonary function testing for risk stratification. It has been suggested that the test simply confirms the clinical impression of disease severity in most cases, adding little to the clinical estimation of risk of complications[25]. Consequently, most patients with an abnormal spirometry test result would also have been identified on the basis of history and physical examination. Several critical remarks can be made. First, lung function measurements and the presence of symptoms are poorly associated[10]. Second, all studies on the added value of preoperative spirometry were conducted in a general population, and not in the specific morbidly obese patient group undergoing bariatric surgery, as described here. Since the morbidly obese can be seen as a distinct group with a different physiol-

ogy, it is questionable whether results from the general population also apply to the obese. One exception is Gonzalez et al. who investigated the role of pulmonary function testing specifically in the morbidly obese. They found that a FEV_1 <80% of predicted increased the likelihood of complicated postoperative management after Roux-en-Y gastric bypass[21]. They combined open and laparoscopic operations, whereas we only used the laparoscopic technique. Although the current study does not support the data by Gonzalez et al, a similar trend was found here (OR 1.9, p=0.07, table 4). However, our study found that FEV_1/FVC <70% (airflow obstruction) and ΔFEV_1>12% (airflow reversibility) increased the likelihood of complicated bariatric surgery.

Airflow reversibility and airflow obstruction are hallmarks of asthma. Valid comparisons with other studies are limited. Other publications on the risk of complications of bariatric surgery did not include asthma[3], or state that well controlled asthma is not a risk factor[8]. Although the diagnosis of asthma is usually based on the presence of characteristic symptoms, in the morbidly obese, these symptoms are often unreliable[26]. It is known that asthma is overdiagnosed by 30% when self-reported asthma is used[27]. The European Respiratory Society state in the Global Initiative for Asthma guidelines, that the measurement of reversibility of lung function abnormalities greatly enhance diagnostic confidence, and it also recommends that patients with asthma undergo preoperative evaluation to assess asthma control[18]. We advocate that spirometry should be part of pre-operative evaluation before bariatric surgery for the following three reasons. First of all, this is because asthma is 50% more prevalent among obese subjects[6], and obesity is an important risk factor for severe asthma[7]. Secondly, the diagnosis of asthma is more complicated in obese subjects than in lean subjects. Finally, our results show that spirometric tests can identify the patients at risk for complications.

Interestingly, our study has shown that spirometry is not only useful in predicting pulmonary complications, but it might predict all complications of bariatric surgery. This it is in line with previous findings that FEV_1 is associated with mortality[28-30]. FEV_1 could possibly be a marker of general health or fitness. So abnormal spirometry does not only indicate obstructive pulmonary disease, but might also indicate poor general health. In contrast to spirometry, the American Society of Anesthesiologists physical status scale (ASA) appeared to be insensitive for predicting complications in this study.

Another study suggested that the super obese (BMI > 50 kg/m^2) are more prone to complications of bariatric surgery[31]. This study did not find this relationship in our cohort, despite the fact that 21% had a BMI > 50 kg/m^2. Furthermore, this study found no difference in mean BMI, body fat percentage or abdominal circumference between the subjects with and without complications. Therefore, this study does not support that differences in fat distribution influence the risk of complications of bariatric surgery.

Cawley and co-workers in a large cohort study showed that subjects with obesity related co-morbidities prior to bariatric surgery were at significantly elevated risk of

post-surgery complications[32]. In contrast, in our cohort pre-surgical obesity-related co-morbidities such as diabetes mellitus, hypertension, hyperlipidemia, GERD or OSAS were unrelated to complications. This might be an effect of the extensive pre-surgical screening -- and if indicated treatment -- for co-morbidities as is standard in our hospital[33].

There are several limitations. First of all, complications were obtained from the patient charts, and may have been subject to underreporting. Secondly, we did not perform methacholine provocation tests, implying that a definite diagnosis of asthma could not always be reached. Finally, we did not perform a randomized study, so we cannot state anything on the surplus value of spirometry. Furthermore, the extensive pre-surgical screening program as incorporated in our hospital could have reduced the incidence of complications. The low numbers of pulmonary complications in our study did not allow for specific subgroup comparisons.

As symptoms are often unreliable in the morbidly obese, pulmonary function tests should routinely be part of the preoperative risk assessment. We have shown that subjects with complications within 30 days of bariatric surgery more often have airflow reversibility or airflow obstruction. Generally laparoscopic bariatric surgery is safe, but randomized prospective studies are needed to investigate whether abnormal pulmonary functions tests could indeed serve as a guide in patient selection and optimization of the preoperative medical condition of patients undergoing bariatric surgery, which could lead to additional improvement in the outcomes after bariatric surgery.

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REFERENCES

1. Organisation WH. Obesity and overweight Fact Sheet no 311. 2011 [cited; Available from: http://www.who.int/mediacentre/factsheets/fs311/en/index.html
2. Buchwald H, Oien DM. Metabolic/bariatric surgery Worldwide 2008. *Obes Surg* 2009;19(12):1605-11.
3. Gupta PK, Gupta H, Kaushik M, Fang X, Miller WJ, Morrow LE, Armour-Forse R. Predictors of pulmonary complications after bariatric surgery. *Surg Obes Relat Dis* 2011;8(5):574-81.
4. Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA, Jr. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. *J Am Coll Surg* 2004;199(4):531-7.
5. Brooks-Brunn JA. Predictors of postoperative pulmonary complications following abdominal surgery. *Chest* 1997;111(3):564-71.
6. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;175(7):661-6.
7. Mosen DM, Schatz M, Magid DJ, Camargo CA, Jr. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol* 2008;122(3):507-11 e6.
8. Smetana GW. Postoperative pulmonary complications: an update on risk assessment and reduction. *Cleve Clin J Med* 2009;76 Suppl 4:S60-5.
9. Chetta A, Tzani P, Marangio E, Carbognani P, Bobbio A, Olivieri D. Respiratory effects of surgery and pulmonary function testing in the preoperative evaluation. *Acta Biomed* 2006;77(2):69-74.
10. Kerstjens HA, Brand PL, de Jong PM, Koeter GH, Postma DS. Influence of treatment on peak expiratory flow and its relation to airway hyperresponsiveness and symptoms. The Dutch CNSLD Study Group. *Thorax* 1994;49(11):1109-15.
11. Hamoui N, Anthone G, Crookes PF. The value of pulmonary function testing prior to bariatric surgery. *Obes Surg* 2006;16(12):1570-3.
12. Reoch J, Mottillo S, Shimony A, Filion KB, Christou NV, Joseph L, Poirier P, Eisenberg MJ. Safety of laparoscopic vs open bariatric surgery: a systematic review and meta-analysis. *Arch Surg* 2011; 146(11):1314-22.
13. Davis G, Patel JA, Gagne DJ. Pulmonary considerations in obesity and the bariatric surgical patient. *Med Clin North Am* 2007;91(3):433-42, xi.
14. Fuller NJ, Sawyer MB, Elia M. Comparative evaluation of body composition methods and predictions, and calculation of density and hydration fraction of fat-free mass, in obese women. *Int J Obes Relat Metab Disord* 1994;18(7):503-12.
15. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109(3):433-8.
16. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540-5.
17. Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, Lind T. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 2009;30(10):1030-8.
18. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005;26(2):319-38.

19. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31(1):143-78.
20. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171(8):912-30.
21. Gadiot RP, Biter LU, Zengerink HJ, de Vos Tot Nederveen Cappel RJ, Elte JW, Castro Cabezas M, Mannaerts GH. Laparoscopic sleeve gastrectomy with an extensive posterior mobilization: technique and preliminary results. *Obes Surg* 2012;22(2):320-9.
22. Gonzalez R, Bowers SP, Venkatesh KR, Lin E, Smith CD. Preoperative factors predictive of complicated postoperative management after Roux-en-Y gastric bypass for morbid obesity. *Surg Endosc* 2003;17(12):1900-4.
23. Pratt GM, Learn CA, Hughes GD, Clark BL, Warthen M, Pories W. Demographics and outcomes at American Society for Metabolic and Bariatric Surgery Centers of Excellence. *Surg Endosc* 2009; 23(4):795-9.
24. Schauer P, Ikramuddin S, Hamad G, Gourash W. The learning curve for laparoscopic Roux-en-Y gastric bypass is 100 cases. *Surg Endosc* 2003;17(2):212-5.
25. Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. *Ann Intern Med* 2006; 144(8):581-95.
26. Babb TG, Ranasinghe KG, Comeau LA, Semon TL, Schwartz B. Dyspnea on exertion in obese women: association with an increased oxygen cost of breathing. *Am J Respir Crit Care Med* 2008; 178(2):116-23.
27. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Doucette S, Fergusson D. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179(11):1121-31.
28. Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur Respir J* 2007;30(4):616-22.
29. Schunemann HJ, Dorn J, Grant BJ, Winkelstein W, Jr., Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest* 2000;118(3):656-64.
30. Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* 2005;127(6):1952-9.
31. Arterburn D, Livingston EH, Schifftner T, Kahwati LC, Henderson WG, Maciejewski ML. Predictors of long-term mortality after bariatric surgery performed in Veterans Affairs medical centers. *Arch Surg* 2009;144(10):914-20.
32. Cawley J, Sweeney MJ, Kurian M, Beane S. Predicting complications after bariatric surgery using obesity-related co-morbidities. *Obes Surg* 2007;17(11):1451-6.
33. Elte JW, Castro Cabezas M, Vrijland WW, Ruseler CH, Groen M, Mannaerts GH. Proposal for a multidisciplinary approach to the patient with morbid obesity: the St. Franciscus Hospital morbid obesity program. *Eur J Intern Med* 2008;19(2):92-8.

7

Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma

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ABSTRACT

Background: The pathogenesis of asthma in obese subjects is poorly understood and has been described as a specific phenotype in these patients. Weight loss improves asthma control and lung function. Whether this improvement is the result of better mechanical properties of the airways or decreased systemic and bronchial inflammation remains unclear.

Methods: A longitudinal study in obese patients with asthma (bariatric surgery and asthma group (BS+A), n=27) and obese control (bariatric surgery without asthma group (BS-A), n=39) subjects undergoing bariatric surgery, and obese patients with asthma without intervention (no bariatric surgery and asthma group (NBS+A), n=12). Lung function, asthma control, cellular infiltrates in bronchial biopsies and circulating markers of systemic inflammation were measured during follow up at 3, 6 and 12 months.

Results: Bariatric surgery resulted in a profound weight loss at 12 months. In the BS+A group as well as the BS-A group FEV_1, functional residual capacity, total lung capacity improved, whereas FEV_1/FVC only improved in the BS-A group. In addition, Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire, inhaled corticosteroid use and PD_{20} improved in BS+A, whereas in the NBS+A group only ACQ improved. Small airway function R_5-R_{20} improved in both surgery groups, however the change in the BS+A group was greater, resulting in a comparable R_5-R_{20} between BS+A and BS-A at 12 month follow-up. Besides improvement of systemic inflammation (hs-CRP, adiponectin and leptin) after BS, only a decrease in mast cell numbers was detectable in the BS+A group.

Conclusions: Bariatric surgery improved small airway function, decreased systemic inflammation and number of mast cells in the airways. These effects could explain the improvement of asthma control, quality of life and lung function. Therefore bariatric surgery, in addition to all other positive effects, also improves asthma in subjects with morbid obesity.

INTRODUCTION

Asthma prevalence has increased over the recent decades[1, 2], concurrently with the prevalence of obesity, suggesting a possible link between obesity and asthma[3]. In a prospective study on the relationship between obesity and asthma, obese patients appeared to have a 2.6 times elevated risk of developing asthma[4]. In addition, obesity is associated with increased severity of asthma. Obese patients with asthma have worse asthma control[5] and respond less to standard therapy compared with lean patients with asthma[6].

A recent position paper on weight loss interventions in asthma[7] concluded that the evidence for benefits from weight reduction on asthma outcomes is weak. Unfortunately, only studies with dietary weight loss were included, and a sustained effect of weight loss through lifestyle changes is small. In contrast, bariatric surgery leads to a more pronounced and persistent weight loss in subjects who are morbidly obese[8]. Therefore, weight loss by bariatric surgery may have more profound effects on asthma.

Asthma in the patients who are obese has been described as a specific phenotype, with high symptom expression and late onset of symptoms[9]. Whether bronchial inflammation in obese subjects with asthma is characterised by eosinophilic or neutrophilic inflammation, or both, is a matter of debate in the literature. Different methods were used to (indirectly) measure bronchial inflammation. So far, only two studies have reported on the analysis of bronchial biopsies in obese subjects with asthma[10, 11], in which, especially in those who are morbidly obese, little inflammation was detectable in the airways. Although previous studies have shown that bariatric surgery does improve asthma control, lung function and systemic inflammation[12-18], the effect on bronchial inflammation is unknown. Previous studies were conducted in small groups and either lacked follow up of a control group [12, 13, 15], or they lacked a non-intervention control group[13, 14, 16-18]. To our knowledge, this is the first study analysing bronchial biopsies before and after bariatric surgery. We hypothesised that bariatric surgery and weight loss would result in improved bronchial obstruction, and reduced systemic and bronchial inflammation. To test this, we performed a cohort study to evaluate the impact of weight loss by bariatric surgery on asthma control, lung function and bronchial and systemic inflammation after 12-month follow-up. Baseline data (including subjects without 12 month follow-up) were published previously[11].

METHODS

Study population

This study is part of a larger study, of which results have been reported before[11, 19] Inclusion and exclusion criteria of this study are described in the online supplementary material. In summary, subjects were between 18 and 50 years old, had a body mass index (BMI) above 35 kg/m^2, and were excluded if they smoked more than 10 cigarettes per day or had smoked more than 10 pack years.

The local ethics committee (Toetsingscommissie Wetenschappenlijk Onderzoek Rotterdam e.o.) approved the study protocol (Netherlands Trial Register 3204), and all subjects gave written informed consent.

The subjects in this study were divided into three groups: a group of morbidly obese subjects with asthma scheduled for bariatric surgery (BS+A), a group of morbidly obese subjects without asthma also scheduled for bariatric surgery (BS-A), and a group of obese subjects with asthma not undergoing bariatric surgery (NBS+A). The first two groups were patients who applied for bariatric surgery in the Sint Franciscus Gasthuis; the third group was a control group included from our outpatient clinic.

The primary endpoint of the study was the change of FEV_1/FVC at 12 month follow-up. Secondary endpoints were other lung function parameters, asthma symptoms (asthma control, asthma-related quality of life, medication use), change of comorbidities (obstructive sleep apnoea syndrome (OSAS), gastro-oesophageal reflux disease) airway inflammation and systemic inflammation at 3, 6 and 12-month follow-up. Only subjects with a follow-up at 12 months were analysed. Baseline data (including subjects without 12-month follow-up) were published previously[11].

Definition of asthma

Asthma was defined according to Global Initiative for Asthma (GINA) guidelines[1] as both the presence of symptoms and either an increase of ≥12% and 200 mL in FEV_1 after salbutamol, or a positive provocation test (methacholine PD_{20} <1.8 mg). Patients without airway reversibility and a negative provocation test formed the control group.

Descriptions of pulmonary function tests (spirometry[20, 21], exhaled nitric oxide[22], impulse oscillometry, diffusion capacity[23] and methacholine provocation testing[24, 25]) can be found in the online supplementary material, along with descriptions of the questionnaires used (Asthma Quality of Life Questionnaire (AQLQ)[26] and Asthma Control Questionnaire (ACQ)[27]), comorbidities (obstructive sleep apnoea syndrome (OSAS)[28], gastro-oesophageal reflux disease[29] and metabolic syndrome[30]), atopy definitions, laboratory measurements and the formula used for the percentage excess weight loss (%EWL).

Bronchial biopsies and immunohistochemistry

Peripheral bronchial biopsies were taken prior to laparoscopic bariatric surgery (either sleeve gastrectomy or Roux-and-Y gastric bypass), after routine anaesthesia with desflurane and remifentanil, directly after intubation[11]. Twelve months after bariatric surgery bronchial biopsies were taken during cosmetic surgery or during an out-patient visit. Bronchoscopy was performed according to the British Thoracic Society guidelines[31] using a flexible fibre optic bronchoscope (Olympus). Four biopsies were taken from the segmental carina from the right middle and lower lobe using a forceps (Boston Scientific, Radial Jaw 3). The 4 µm sections from paraffin-embedded bronchial biopsies were stained for EG2 (eosinophils), neutrophil elastase (neutrophils), AA1 (mast cells), CD68 (macrophages), CD20 (B cells), CD8, CD4 and CD3 (T cells), or negative control, and enumerated as cells per square millimetre submucosa on digitalised images. The smallest 10% of selected surfaces of biopsies were not used for analysis. The mean cell count of an individual was the mean of two to four biopsies. The observer was blinded with regard to the patient's number and clinical status during selection, processing and analysis of the biopsy samples. Baseline data were published previously[11].

Power calculation and statistical analysis

The group size was powered on the expected change in FEV_1/FVC ratio after bariatric surgery. Based on a pilot study and published data we assumed that in the BS+A group the FEV_1/FVC ratio would increase from 72% to 75% (SD ± 6). The increase of 3% represents an effect size of 0.5. To find a difference in the group with obesity and asthma before and after operation with an α error of 5% and a power of 80%, we needed at least 27 participants per group. With an expected drop-out of 25% over 1-year follow-up we aimed at 40 patients per subgroup.

For the comparison between the three groups at baseline, the independent samples median test for scaled data or the Chi-square or Fisher exact test were used. For all groups, baseline data were compared with 12-month follow-up data, using a non-parametric test (related-samples Wilcoxon signed rank test). Unless indicated otherwise, all data are expressed as median (min-max) for paired data for scale variables or percentage for categorical variables. Spearman correlation coefficient (R) was calculated. All analyses were performed using SPSS V.21.0 software (SPSS Inc., Chicago, Illinois, USA). Given the exploratory nature of this study, we did not control for multiple comparisons. Results were evaluated at 95% CI at a two-sided significance threshold of $p<0.05$.

RESULTS

A total of 101 patients were included in the initial study[11]. At 12-month follow-up data were available for 78 subjects, which were included in the present analysis. In table 1 (and online supplementary table S1B) the baseline subject characteristics are shown (27 BS+A, 39 BS-A and 12 NBS+A). There were no significant differences in demographic characteristics between the groups, with the exception of BMI.

Table 1 Demographics of the study population

	NBS+A	BS+A	BS-A	p Value
Number				
Baseline	12	27	39	
3-month follow-up	11	26	33	
6-month follow-up	11	21	34	
12-month follow-up	12	27	39	
Gender (%female)	91.7%	74.1	82.1	0.494
Ethnicity (%non-Caucasian)	25.0%	14.8%	15.4%	0.714
Age (years)	33 (20-45)	36 (19-48)	39 (18-50)	0.440
Weight (kg)	103 (82-132)	130 (101-202)	126 (94-199)	0.044
Body mass index (kg/m^2)	35.6 (30.9-53.9)	45.1 (38.4-63.8)	43.1 (35.6-58.6)	0.015
Abdominal circumference (cm)	119 (102-155)	133 (112-165)	127 (103-200)	0.016
Smoking status				0.178
% never smoked	75.0%	55.6%	71.8%	
% stopped smoking	16.7%	11.1%	17.9%	
% current smoker	8.3%	33.3%	10.3%	
Pack years	0 (0-0)	0 (0-10)	0 (0-10)	0.311
Asthma				
Asthma Control Questionnaire[1]	1.7 (0.3-2.6)	1.1 (0.4-2.9)	0.3 (0-2.9)	<0.001
Asthma Quality of Life Questionnaire [2]	5.4 (3.5-6.7)	5.6 (3.7-6.8)	6.5 (3.7-7.0)	0.007
Lung function				
Spirometry				
FEV_1, pre(% predicted)	88 (45-106)	86 (66-119)	97 (73-125)	0.009
FEV_1, post (% predicted)	95 (49-106)	93 (75-118)	101 (75-129)	0.079
FVC, pre (% predicted)	102 (64-118)	97 (75-126)	106 (77-144)	0.575
FVC, post (% predicted)	107 (62-120)	99 (74-126)	107 (78-141)	0.754
FEV1/FVC, pre (%)	79 (61-90)	76 (63-92)	81 (66-93)	0.096
FEV1/FVC, post (%)	82 (69-91)	79 (67-94)	84 (68-94)	0.215
RV, post (% predicted) *	79.5 (74-92)	74 (39-126)	74 (47-118)	0.567
TLC, post (% predicted) *	92.5 (77-109)	98 (83-106)	95 (75-114)	0.826
FRC, post (% predicted) *	68 (54-90)	62 (40-95)	64 (41-88)	0.554
RV/TLC, post (%) *	26.5 (20-36)	22 (10-41)	24 (12-41)	0.146

Table 1 Demographics of the study population (continued)

	NBS+A	BS+A	BS-A	p Value
Number				
Reversibility FEV_1	7 (-12-22)	9 (-6-20)	4 (-7 -11)	0.012
Fe_{NO} (ppb)	17 (7-96)	16 (5-45)	16 (7-53)	0.870
Diffusion capacity, kCo (% predicted)	98 (70-116)	97 (69-133)	95 (69-134)	0.890
PD_{20} (mg)	0.31 (0.04-1.8)	0.37 (0.04-1.8)	1.8 (1.8-1.8)	
IOS				
R_5 (kPa/sec)	0.58 (0.24-1.11)	0.69 (0.41-1.39)	0.57 (0.17-0.97)	0.022
R_{20} (kPa/sec)	0.44 (0.20-0.65)	0.45 (0.27-1.03)	0.43 (0.18-0.68)	0.841
R_5-R_{20} (kPa/sec)	0.18 (0.04-0.62)	0.25 (0.06-0.66)	0.17 (-0.1-0.48)	0.001
X_5 (kPa/sec)	-0.16 (-0.67 to -0.1)	-0.26 (0.87 to -0.12)	-0.21 (-0.43 to -0.10)	0.138
F_{res} (Hz)	17.3 (9.2-30.4)	22.6 (10.7-28.9)	18.5 (8.4-28.7)	0.001

Data are presented as median (min-max)

[1] Scores of the Asthma Control Questionnaire range from 0 to 6, with lower scores indicating better asthma control

[2] Scores of the Asthma Quality of Life Questionnaire range from 1 to 7, with higher scores indicating better asthma-specific quality of life

* Because of weight limitations for the body box (<150 kg), full spirometry could not be performed in all subjects; numbers for these parameters: NBS+A =4, BS+A = 15, BS-A = 30

BS+A, bariatric surgery and asthma group; BS-A, bariatric surgery without asthma group; Fe_{NO}, exhaled nitric oxide; FRC, functional residual capacity; IOS, impulse oscillometry; NBS+A, no bariatric surgery and asthma group; PD_{20}, provocative dose of methacholine inducing a 20% fall in FEV_1; RV, residual volume; TLC, total lung capacity

Weight loss

Sixty-three percent of the BS+A and 69% of the BS-A group underwent gastric sleeve resection; the remaining subjects underwent gastric bypass surgery. BMI and abdominal circumference decreased in both bariatric surgery groups, and remained stable in the non-intervention group (figure 1A, B). Although the %EWL was significantly lower in the BS+A group compared with the BS-A group (median 73% vs 84% respectively, p=0.045), the BMI did not differ between the BS+A and BS-A group at baseline or at 12-month follow-up.

Effect of weight loss on lung function tests

Figure 2 and table 2 show the results of the follow-up of lung function. Twelve months after bariatric surgery FEV_1/FVC and residual volume (RV) improved only in the BS-A group, whereas FEV_1 (post), functional residual capacity (FRC), and total lung capacity (TLC) improved in both BS-A and BS+A groups. These results can be better explained by a reduction in lung restriction than by a reduction in lung obstruction. RV/TLC, representing hyperinflation, did not change in any of the groups. FEV_1/FVC, RV, FEV_1,

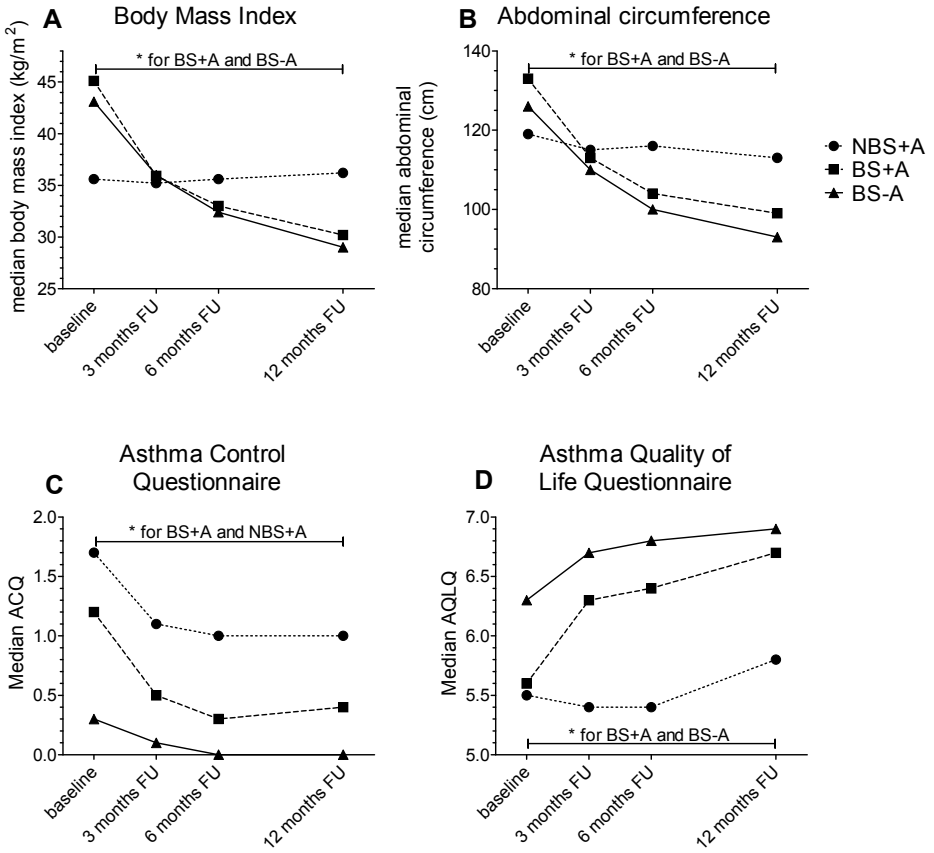

Figure 1 Effect of weight loss on asthma control

NBS+A, no bariatric surgery and asthma group (circles); BS+A, bariatric surgery and asthma group (squares); BS-A = bariatric surgery without asthma group (triangles). Only p-values for comparison between baseline and 12-month follow-up were calculated; only significant p-values are shown (*).

Scores of the Asthma Control Questionnaire (ACQ) range from 0 to 6, with lower scores indicating better asthma control. Scores of the Asthma Quality of Life Questionnaire (AQLQ) range from 1 to 7, with higher scores indicating better asthma-specific quality of life. FU, follow-up.

FRC and TLC did not change in the NBS+A group, confirming that the improvement in restrictive lung function was due to weight loss. There was no significant change in diffusion capacity or exhaled nitric oxide (Fe_{NO}) in any of the groups.

Impulse oscillometry, and especially R_5-R_{20} as a measure of small airway function, showed a significant improvement in both bariatric groups (figure 2-C). At baseline the BS+A group had a significantly higher R_5-R_{20} as compared with the BS-A group ($p<0.001$). At 12-month follow-up the R_5-R_{20} of the BS+A group was comparable to the BS-A group. We found a correlation between BMI and R_5-R_{20} ($R=0.518$, $p<0.001$), and abdominal circumference and R_5-R_{20} ($R=0.415$, $p<0.001$). Also between ACQ and R_5-R_{20} ($R=0.498$, $p<0.001$) and ACQ and BMI ($R=0.374$, $p<0.001$) (figure 3).

Table 2 Effect of bariatric surgery on lung function

	NBS+A			BS+A			BS-A		
	Baseline	**12-month FU**	**p Value[1]**	**Baseline**	**12-month FU**	**p Value[1]**	**Baseline**	**12-month FU**	**p Value[1]**
Spirometry									
FEV_1, pre (% predicted)	88 (45-106)	81 (71-117)	0.553	86 (66-119)	95 (67-119)	<0.001	97 (73-125)	106 (75-134)	<0.001
FEV_1, post (% predicted)	95 (49-106)	88 (70-118)	0.759	93 (75-118)	100 (79-117)	0.001	101 (75-129)	108 (80-139)	<0.001
FVC, pre (% predicted)	102 (64-118)	103 (77-131)	0.683	96 (75-126)	105 (75-131)	0.001	106 (77-144)	109 (87-149)	0.009
FVC, post (% predicted)	107 (62-120)	106 (78-131)	0.721	99 (74-126)	107 (77-123)	0.002	107 (78-141)	107 (84-149)	0.046
FEV1/FVC, pre (%)	79 (61-90)	78 (63-83)	0.550	76 (63-92)	77 (57-92)	0.246	81 (66-93)	83 (73-99)	0.021
FEV1/FVC, post (%)	82 (69-91)	78 (66-86)	0.239	79 (67-94)	81 (69-94)	0.327	84 (68-94)	87 (77-98)	<0.001
RV, post (% predicted) *	79 (74-92)	65 (55-105)	0.285	80 (39-126)	79 (76-115)	0.789	72 (47-96)	82 (43-137)	0.013
TLC, post (% predicted) *	83 (77-102)	87 (74-105)	0.414	6 (83-106)	104 (79-115)	0.018	96 (75-114)	101 (81-122)	<0.001
FRC, post (% predicted) *	65 (54-90)	69 (61-85)	0.593	62 (40-95)	88 (53-117)	0.008	64 (41-77)	94 (59-145)	<0.001
RV/TLC, post (%) *	28 (25-36)	22 (20-40)	0.285	20 (10-41)	22 (15-29)	0.767	25 (15-33)	28 (11-40)	0.054
Fe_{NO} (ppb) **	16 (7-96)	14 (8-58)	0.097	18 (8-45)	15 (8-32)	0.477	15 (7-53)	14 (5-67)	0.687
Diffusion capacity, kCO (% predicted)	98 (70-116)	95 (71-136)	0.202	97 (69-133)	99 (67-118)	0.483	95 (77-134)	91 (69-127)	0.179
PD_{20} methacholine (mg)	0.23 (0.09-1.31)	0.92 (0.19-1.8)	0.273	0.22 (0.04-1.40)	1.46 (0.04-1.8)	0.001			

Data are presented as median (min-max)

[1] p Value for comparison baseline versus 12 months follow up within each group

* Because of weight limitations for the body box (<150 kg), full spirometry could not be performed in all subjects; numbers for these parameters: NBS+A =3, BS+A = 12, BS-A = 27

BS+A, bariatric surgery and asthma group; BS-A, bariatric surgery without asthma group; Fe_{NO}, exhaled nitric oxide; FRC, functional residual capacity; FU, follow-up; NBS+A, no bariatric surgery and asthma group; PD_{20}, provocative dose of methacholine inducing a 20% fall in FEV_1; RV, residual volume; TLC, total lung capacity

In the BS+A group, 24 subjects had a positive provocation test at baseline (PD_{20} < 1.8 mg). At 3, 6 and 12-month follow-up of these 24 subjects, 11 (of 24), 9 (of 20) and 13 (of 25) subjects had a negative provocation test, respectively. Median values increased significantly (figure 2-D and table 2). In the NBS+A group the PD_{20} did not increase significantly. No correlation was found between PD_{20} and BMI, however we did found a significant correlation between PD_{20} and R_5-R_{20} (R= -0.337, p<0.001).

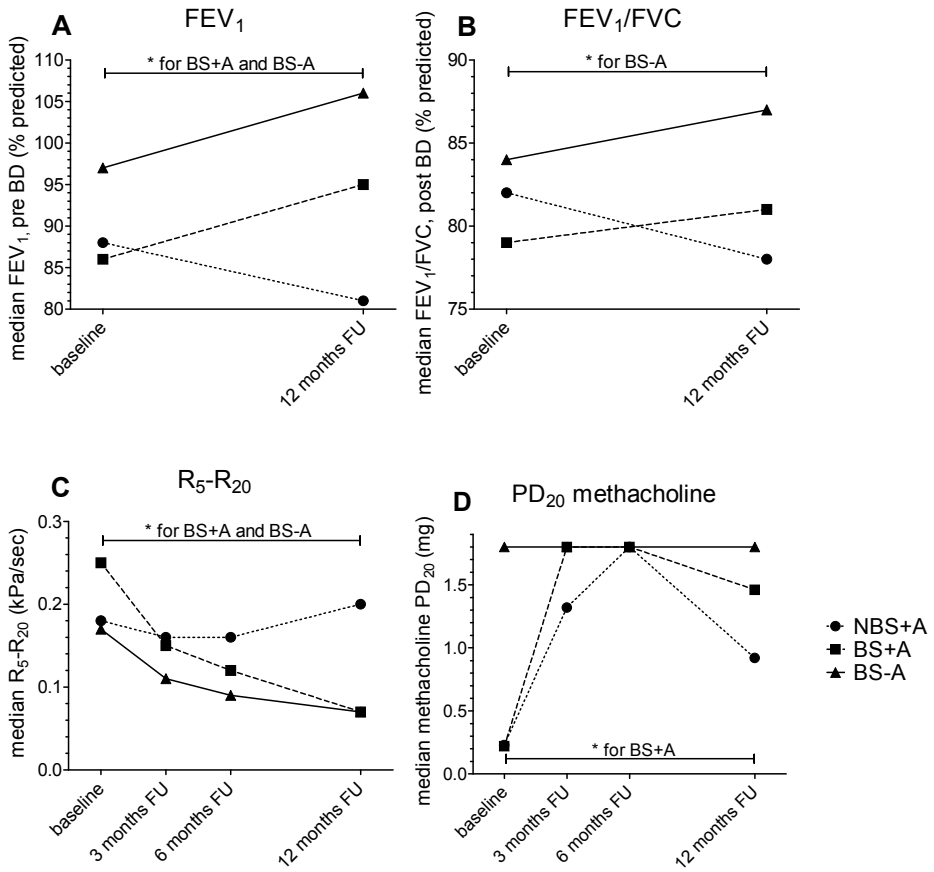

Figure 2 Effect of weight loss on lung function

NBS+A, no bariatric surgery and asthma group (circles); BS+A, bariatric surgery and asthma group (squares); BS-A, bariatric surgery without asthma group (triangles). Only p-values for comparison between baseline and 12-month follow-up were calculated, only significant p-values are shown (*)

(A) FEV_1 BS+A median 97 – 106 % predicted, p=0.001; BS-A median 86 - 95 % predicted, p< 0.001; (B) FEV_1/FVC BS-A 84 - 87%, p<0.001; (C) R_5-R_{20} BS+A 0.25 - 0.07 kPa/sec, p<0.001; BS-A 0.17 - 0.07 kPa/sec; p<0.001. While there was at baseline a significant difference in R_5-R_{20} between BS+A and BS-A group (p<0.001), at 12-month follow-up there was no significant difference (p=0.919); (D) PD_{20} BS+A median 0.22 - 1.46 mg, p=0.001.

Effect of weight loss on asthma control

The ACQ improved statistically and was clinically significant (Δ>0.5) in both asthma groups (NBS+A and BS+A) at 12-month follow-up (figure 1-C). The improvement in ACQ in the BS-A group was also statistically significant, but not clinically significant.

The AQLQ did not improve in the NBS+A group, but it did improve in the BS+A group (statistically and clinically significant (Δ>0.5)) at 12-month follow-up, and also in the BS-A group (figure 1-D).

Medication use

In the BS+A group 10 subjects used inhaled corticosteroids (ICS) at inclusion in the study, of which 8 subjects agreed to stop for at least 6 weeks before provocation testing. Because of symptoms, one subject restarted ICS, and three subjects who did not use ICS before inclusion in the study were prescribed ICS because of progression of symptoms. So, a total of six subjects used ICS at baseline, with a median budesonide equivalence dose of 600 µg/day. At 12-month follow-up, ICS was prescribed to six subjects, however only four subjects used the ICS, with a median budesonide equivalence of 600 µg/ day.

In the NBS+A group all 12 subjects used ICS at baseline, and in follow-up all subjects remained on ICS: the median budesonide equivalence dose remained stable (baseline 800 µg, 3 months 400 µg and 12 months 800 µg).

Comorbidities and activity

There were no significant changes in the Epworth Sleepiness Scale or Gastro-oesophageal Reflux Disease questionnaire in any group at any follow-up time point (3, 6 or 12 months) (data not shown). Daily activity as assessed by the number of steps a day did improve significantly in both bariatric surgery groups at 12-month follow-up (BS+A: median 4946 to 8312, p=0.030; BS-A: median 5224 to 8094, p= 0.005), and did not improve in the NBS+A group.

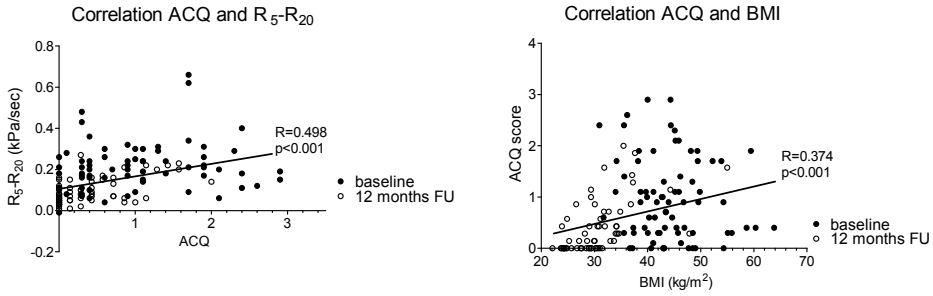

Figure 3 Correlation analysis of asthma control, small airway function and body mass index
Baseline data and 12-month follow-up data were used to calculate correlations. ACQ, Asthma Control Questionnaire.

Effect of weight loss on bronchial and systemic inflammation

Interleukine (IL)-6, IL-8, tumor necrosis factor (TNF)-α and granulocyte macrophage colony-stimulating factor (GM-CSF), markers of systemic inflammation, did not change at follow-up in any of the groups, although the levels of IL-6, TNFα and GM-CSF were at the lower limit of detection. Other markers of systemic inflammation, such as high-sensitivity C-reactive protein (hs-CRP), leptin and adiponectin, were significantly changed at 12-month follow-up in both the BS+A, and BS-A groups, and did not change in the NBS+A group (table 3).

At 12-month follow-up, bronchial biopsies were collected from 24 subjects (8 BS+A, 14 BS-A). Submucosal cell counts of eosinophils (EG2), neutrophils (NE), B cells (CD20), macrophages (CD68), $CD4^+$ T-cells or $CD8^+$ T cells did not change at 12-month follow-up in either the BS+A or BS-A group (figure 4, and online supplementary table S4). In contrast, mast cells (AA1) decreased significantly at 12-month follow-up in the BS+A group (median 118-61 cells/mm^2, p=0.036), whereas $CD3^+$ T cells decreased significantly at 12-month follow-up only in the BS-A group (median 884 - 558 cells/mm^2, p=0.015).

Subgroup analysis

When we divided the BS+A group into subjects who at baseline had a positive provocation test, and at 12-month follow-up either a positive (non-responder) or negative (responder) provocation test, we found no differences between the two groups. In a subgroup analysis of patients with low immunoglobulin E (IgE) ('T_H2-low', IgE <100, n=6) versus high IgE ('T_H2-high', n=12), we found that the PD_{20} only improved in the IgE-high group at 12-month follow-up (median 0.19 - 1.59 mg, p=0.003), and not in the IgE-low group (median 0.53 - 0.99 mg). We found no differences in change in R_5-R_{20}.

DISCUSSION

In the present study bariatric surgery of morbidly obese patients with asthma was found to result in a significant improvement in small airway function (R_5-R_{20}) and airway hyperresponsiveness (PD_{20} methacholine), as well as asthma control and markers of bronchial (mast cell counts) and systemic inflammation. In contrast, there was no change in FEV_1/FVC.

There was no significant improvement in our primary endpoint FEV_1/FVC, a marker of airway obstruction, in the BS+A group. However, in the BS-A group, there was a statistically significant increased FEV_1/FVC, showing that weight loss affects airway diameter to some extent in patients without asthma. As the power of this study should be adequate, we might conclude that weight loss does not influence obstruction of the larger airways in asthma subjects. In line with previous reports[13, 15], we found that weight loss induces

Table 3 Markers of systemic inflammation

	NBS+A				BS+A				BS-A			
	Baseline	**6-month FU**	**12-month FU**	**p Value[1]**	**Baseline**	**6-month FU**	**12-month FU**	**p Value[1]**	**Baseline**	**6-month FU**	**12-month FU**	**p Value[1]**
hs-CRP (ng/mL)	34.4 (1.3-142.0)	49.8 (20.0-142.0)	32.6 (8.5-142.0)	0.953	36.0 (4.3-142.0)	10.1 (1.8-75.6)	7.1 (0.8-139.5)	<0.001	30.4 (0.1-87.0)	13.8 (0.1-51.5)	5.3 (0.8-35.2)	<0.001
IL-6 (pg/mL)	0.7 (0.7-0.9)	0.7 (0.7-6.3)	0.7 (0.7-7.6)	0.655	0.7 (0.7-2.1)	0.7 (0.7-6.9)	0.7 (0.7-5.1)	0.211	0.7 (0.7-13.3)	0.7 (0.7-1.1)	0.7 (0.7-0.8)	0.017
IL-8 (pg/mL)	4.1 (3.0-6.6)	3.9 (1.9-7.3)	4.8 (1.8-8.7)	0.799	3.9 (2.7-13.5)	4.3 (2.4-10.0)	4.8 (1.2-13.3)	0.124	4.0 (1.9-9.1)	4.2 (0.7-7.5)	3.8 (2.1-7.8)	0.225
TNFα (pg/mL)	0.8 (0.8-0.8)	0.8 (0.8-2.8)	0.8 (0.8-2.9)	0.180	0.8 (0.8-1.3)	0.8 (0.8-3.0)	0.8 (0.8-2.4)	0.715	0.8 (0.8-1.0)	0.8 (0.8-1.5)	0.8 (0.8-0.8)	0.180
GM-CSF (pg/mL)	0.6 (0.6-1.7)	0.6 (0.6-26.8)	0.6 (0.6-9.4)	0.686	0.6 (0.6-3.9)	0.6 (0.6-11.5)	0.6 (0.6-3.5)	0.401	0.6 (0.6-0.6)	0.6 (0.6-0.9)	0.6 (0.6-1.5)	0.180
Adiponectin (ng/mL)	10.4 (7.0-17.7)	14.3 (5.9-246.9)	11.2 (5.7-235.6)	0.241	12.0 (4.5-22.0)	17.0 (8.8-1000.0)	22.5 (9.7-1000.0)	<0.001	14.1 (0.06-28.9)	17.6 (7.8-31.9)	23.3 (5.2-40.0)	<0.001
Leptin (ng/mL)	42 (2-97)	54 (4-100)	54 (3-86)	0.721	69 (18-100)	18 (2-98)	11 (0.2-69)	<0.001	55 (11 -100)	7 (0.7-43)	6 (0.2-68)	<0.001

Data are presented as median (min-max)

[1]p Value for comparison baseline versus 12 months follow up within each group (related-samples Wilcoxon signed rank test)

BS+A, bariatric surgery and asthma group; BS-A, bariatric surgery without asthma group; FU, follow-up; GM-CSF, granulocyte macrophage colony-stimulating factor; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; NBS+A, no bariatric surgery and asthma group; TNF, tumour necrosis factor

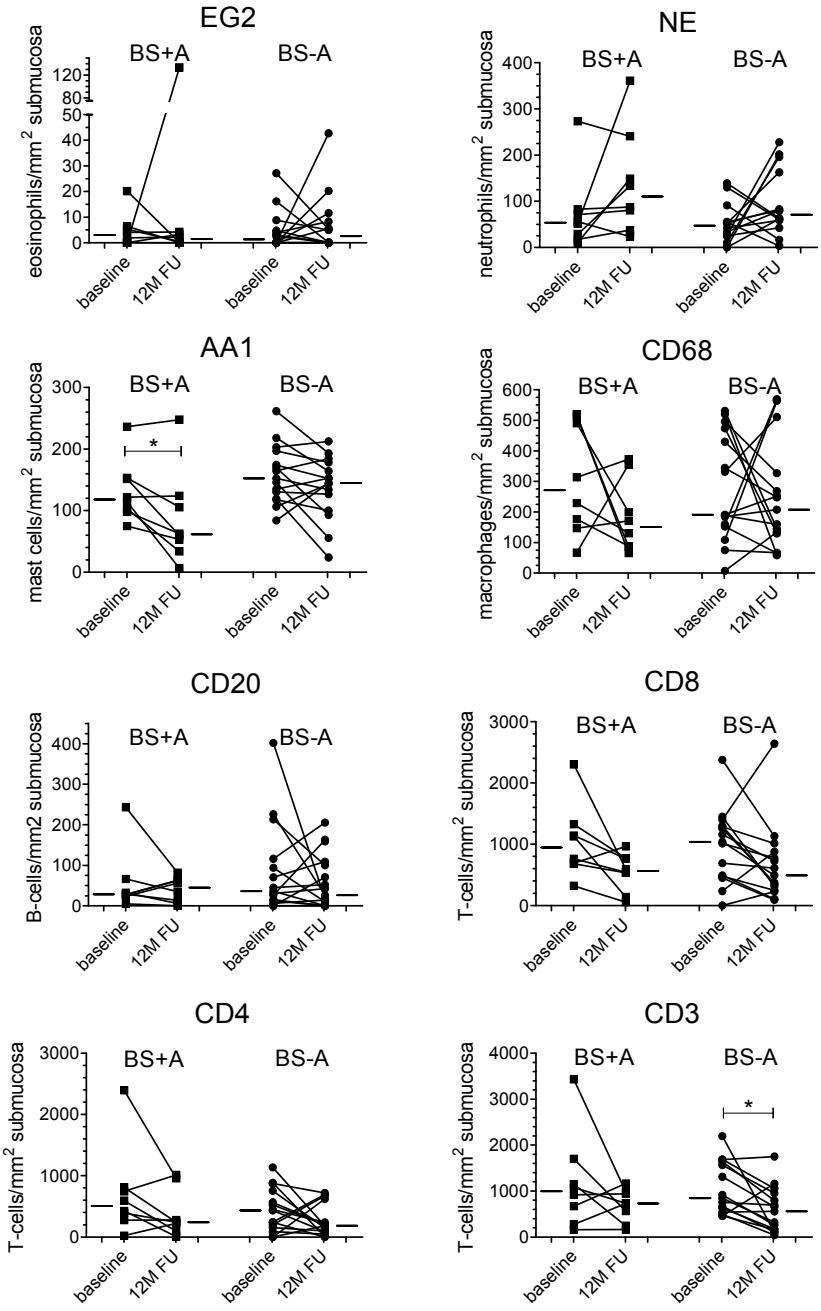

Figure 4 Submucosal cell counts of bronchial biopsies, before and 12 months after bariatric surgery
Bronchial submucosal cell count in morbidly obese subjects before and 12 months after bariatric surgery, with (BS+A, n=8, squares) and without asthma (BS-A, n=14, circles). P Values were calculated for the comparison between baseline and 12-month follow-up (12M FU) within each group, only significant p values are shown (*). Horizontal line represents median.

an increase not only in TLC, but also FRC in both bariatric surgery groups suggesting that the weight loss improves the relative restrictive lung function. Remarkably, the RV in the BS+A group did not change after bariatric surgery, whereas it did in the BS-A group. This could be because the RV at baseline was already relatively high in the BS+A group, so further improvement was unlikely. Perhaps the BS+A group had peripheral airway obstruction before bariatric surgery due to different fat distribution compared with the BS-A group, since the abdominal circumference is higher in the BS+A group. However, the RV/TLC ratio was the same in both bariatric groups, making a difference in obstruction less likely.

The main improvement in lung function was in R_5-R_{20}, a marker of small airway function. Whereas at baseline the R_5-R_{20} in the BS+A group was significantly worse compared with the BS-A group, 12 months after bariatric surgery, there was no longer a significant difference between the two groups. This remained when only non-smokers were analysed (data not shown). Our data are in line with Al-Alwan *et al.*, who recently demonstrated that obese subjects with asthma have more collapsible peripheral airways than obese subjects without asthma[16], suggesting that altered lung mechanics play a role in the relationship between obesity and asthma. In addition to a correlation between R_5-R_{20} and BMI, we also found a correlation between R_5-R_{20} and ACQ, suggesting that increased R_5-R_{20} might explain the high symptom expression in obese subjects with asthma. Dixon *et al.* have shown previously that bariatric surgery was more beneficial to subjects with normal IgE levels (T_H2-low) in contrast to T_H2-high subjects[13], especially for small airway function[18]. In contrast, the present study could not find a relation between IgE levels and small airway function, and only found a relation in the high IgE group and bronchial hyperresponsiveness. Besides a difference in BMI between Dixon and our study (51 and 45 kg/m^2), the IgE level of our 'T_H2 high' group was higher, and the ratio of number of subjects in the low versus high group was different in our study compared with Dixon.

Whereas other studies have shown only a reduction in bronchial hyperreactivity 12 months after bariatric surgery[13, 15], in some of our patients the PD_{20} methacholine became negative, despite the decreased use of ICS in the 12-month follow-up. This was in contrast to the NBS+A subjects, in whom we did not succeed to taper off the ICS. Whether they truly needed ICS is questionable. We found a negative correlation between R_5-R_{20} and PD_{20}, suggesting that the increased peripheral airway resistance is associated with more severe bronchial hyperreactivity.

One hypothesis explaining the relationship between obesity and asthma is the concept of spill over of systemic inflammation caused by obesity, to the lungs, resulting in bronchial inflammation. Although others have demonstrated that obese subjects with asthma have more neutrophilic inflammation compared with lean subjects with asthma[32, 33], we have previously shown that there is no difference in neutrophil (or eosinophil) cell counts in bronchial biopsies between morbidly obese subjects with

asthma and morbidly obese controls[11]. As we found no differences in cell counts at baseline, we expected no change in any cell count after bariatric surgery. However, our results demonstrate that in subjects with asthma, mast cell counts in bronchial biopsies taken 12 months after bariatric surgery decreased significantly compared with baseline. This decrease in mast cells might reflect a better asthma control. This decrease in mast cells could in part explain the improved asthma control, because mast cells contribute to inflammation and tissue remodelling in asthma. As the study was powered to detect changes in the primary endpoint FEV_1/FVC it could be that the number of patients investigated was not enough to detect subtle changes in bronchial inflammatory cells. Still none of the comparisons in cells counts showed a trend of being statistically different. Moreover, we found no differences in demographics between the group with follow-up bronchoscopy and those without (data not shown).

In line with previous reports[34], we found that systemic inflammation (hs-CRP, leptin and adiponectin in serum) decreased after bariatric surgery. These data suggest that a reduction in systemic inflammation may result in reduction in local airway inflammation in subjects with asthma. However, the improvement after weight loss of especially the small airway function, and the correlation between small airway function and ACQ reflects that bariatric surgery also improves the mechanical properties of the lungs. The observation that some obese patients develop asthma and other obese subjects do not has led to several hypotheses. Our data are in line with the suggestion made by Dixon *et al*[16], that obese subjects with asthma may be predisposed to the effect of obesity on small airways, which is supported by their data obtained by computational remodelling of airway wall stiffness and thickness, predicting a relationship between airway hyperresponsiveness and BMI[35].

The strengths of our study are that we included an obese control group of subjects without asthma, as well as a control group of obese subjects with asthma without bariatric surgery. In addition, the group size in our study was larger than previous studies, and we not only performed data collection at 12 months but also at 3 and 6 months of follow-up. Furthermore, the diagnosis of asthma was performed strictly according to the GINA guidelines as a doctor diagnosis of asthma in which symptoms play a major role has previously been shown to be not suitable for diagnosing asthma in patients with obesity[19, 36]. Finally, participation was good and only few dropped out during the 12-month follow-up.

There are also some limitations to our study. First of all, we did not include a lean asthma group. Second, our obese asthma group without bariatric surgery is not fully comparable to both bariatric surgery groups due to differences in recruitment strategy. As a result, for example, the BMI is lower and this is because the frequency of patients with morbid obesity and asthma is low in our outpatient clinic is because the frequency of patients with morbid obesity and asthma is low in our out-patient clinic. As a second

bronchoscopy was optional, a bias is possible. Finally, bronchial biopsies were taken *centrally*, and therefore are not optimally suited to establish a possible relationship with *peripheral* airway function.

In summary, this is the first study that examined a wide variety of clinical, physiological, systemic and bronchial mucosal inflammatory parameters before and after bariatric surgery in morbidly obese subjects with asthma and morbidly obese control subjects. Although we found no improvement in our primary endpoint FEV_1/FVC, we did find improvement in asthma control, quality of life, medication use and PD_{20} methacholine. The significant improvement of R_5-R_{20} (peripheral airway function) after bariatric surgery, which was associated with BMI, ACQ and PD_{20}, suggests that peripheral airways play a major role in the relationship between obesity and asthma. Finally, bariatric surgery also decreased markers of systemic inflammation, and mast cell counts in central bronchial submucosa of obese subject with asthma. Collectively these findings emphasise that weight loss as achieved by bariatric surgery should be a cornerstone in the treatment of morbidly obese patients with asthma. Further research regarding the role of small airways in obese asthma is needed.

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REFERENCES

1. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31(1):143-78.
2. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355(21):2226-35.
3. Chinn S. Asthma and obesity: where are we now? *Thorax* 2003;58(12):1008-10.
4. Camargo CA, Jr., Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;159(21):2582-8.
5. Mosen DM, Schatz M, Magid DJ, Camargo CA, Jr. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol* 2008;122(3):507-11 e6.
6. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DY. Body mass and glucocorticoid response in asthma. *Am J Respir Crit Care Med* 2008;178(7):682-7.
7. Moreira A, Bonini M, Garcia-Larsen V, Bonini S, Del Giacco SR, Agache I, Fonseca J, Papadopoulos NG, Carlsen KH, Delgado L, Haahtela T. Weight loss interventions in asthma: EAACI evidence-based clinical practice guideline (part I). *Allergy*;68(4):425-39.
8. Kushner RF. Clinical assessment and management of adult obesity. *Circulation* 2012;126(24): 2870-7.
9. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178(3):218-24.
10. Desai D, Newby C, Symon FA, Haldar P, Shah S, Gupta S, Bafadhel M, Singapuri A, Siddiqui S, Woods J, Herath A, Anderson IK, Bradding P, Green R, Kulkarni N, Pavord I, Marshall RP, Sousa AR, May RD, Wardlaw AJ, Brightling CE. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. *Am J Respir Crit Care Med* 2013;188(6):657-63.
11. van Huisstede A, Rudolphus A, van Schadewijk A, Cabezas MC, Mannaerts GH, Taube C, Hiemstra PS, Braunstahl GJ. Bronchial and systemic inflammation in morbidly obese subjects with asthma: a biopsy study. *Am J Respir Crit Care Med* 2014;190(8):951-4.
12. Maniscalco M, Zedda A, Faraone S, Cerbone MR, Cristiano S, Giardiello C, Sofia M. Weight loss and asthma control in severely obese asthmatic females. *Respir Med* 2008;102(1):102-8.
13. Dixon AE, Pratley RE, Forgione PM, Kaminsky DA, Whittaker-Leclair LA, Griffes LA, Garudathri J, Raymond D, Poynter ME, Bunn JY, Irvin CG. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011;128(3):508-15 e1-2.
14. Lombardi C, Gargioni S, Gardinazzi A, Canonica GW, Passalacqua G. Impact of bariatric surgery on pulmonary function and nitric oxide in asthmatic and non-asthmatic obese patients. *J Asthma* 2011;48(6):553-7.
15. Boulet LP, Turcotte H, Martin J, Poirier P. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respir Med* 2012;106(5):651-60.
16. Al-Alwan A, Bates JH, Chapman DG, Kaminsky DA, DeSarno MJ, Irvin CG, Dixon AE. The nonallergic asthma of obesity. A matter of distal lung compliance. *Am J Respir Crit Care Med* 2014;189(12): 1494-502.
17. Sideleva O, Suratt BT, Black KE, Tharp WG, Pratley RE, Forgione P, Dienz O, Irvin CG, Dixon AE. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. *Am J Respir Crit Care Med* 2012;186(7):598-605.

18. Chapman DG, Irvin CG, Kaminsky DA, Forgione PM, Bates JH, Dixon AE. Influence of distinct asthma phenotypes on lung function following weight loss in the obese. *Respirology* 2014;19(8): 1170-7.
19. van Huisstede A, Castro Cabezas M, van de Geijn GJ, Mannaerts GH, Njo TL, Taube C, Hiemstra PS, Braunstahl GJ. Underdiagnosis and overdiagnosis of asthma in the morbidly obese. *Respir Med* 2013;107(9):1356-64.
20. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005;26(2):319-38.
21. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5-40.
22. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171(8):912-30.
23. Huang YC, O'Brien SR, MacIntyre NR. Intrabreath diffusing capacity of the lung in healthy individuals at rest and during exercise. *Chest* 2002;122(1):177-85.
24. Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O'Byrne PM, Anderson SD, Juniper EF, Malo JL. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:53-83.
25. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, Cockcroft DW, Fish JE, Sterk PJ. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;161(1):309-29.
26. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14(1):32-8.
27. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14(4):902-7.
28. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540-5.
29. Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, Lind T. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 2009;30(10):1030-8.
30. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109(3):433-8.
31. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. *Thorax* 2001;56 Suppl 1: i1-21.
32. Telenga ED, Tideman SW, Kerstjens HA, Hacken NH, Timens W, Postma DS, van den Berge M. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. *Allergy* 2012;67(8):1060-8.

33. Todd DC, Armstrong S, D'Silva L, Allen CJ, Hargreave FE, Parameswaran K. Effect of obesity on airway inflammation: a cross-sectional analysis of body mass index and sputum cell counts. *Clin Exp Allergy* 2007;37(7):1049-54.
34. Kim SH, Sutherland ER, Gelfand EW. Is there a link between obesity and asthma? *Allergy Asthma Immunol Res* 2014;6(3):189-95.
35. Bates JH, Dixon AE. Potential role of the airway wall in the asthma of obesity. *J Appl Physiol (1985)* 2015;118(1):36-41.
36. Scott S, Currie J, Albert P, Calverley P, Wilding JP. Risk of mis-diagnosis, Health related Quality of Life and Body Mass Index in Overweight Patients with doctor diagnosed asthma. *Chest* 2012; 141(3):616-24.

SUPPLEMENT

METHODS

The subjects included in this study were patients who underwent pre-operative screening before bariatric surgery in the Sint Franciscus Gasthuis in Rotterdam, the Netherlands from September 2009 to April 2011. Eligibility criteria for bariatric surgery were: age between 18 and 60 years old, body mass index (BMI) ≥ 35 kg/m^2. We excluded people who (a) were older than 50 years of age or; (b) had a history of smoking more than 10 cigarettes a day, or were currently smoking more than 10 cigarettes a day (with the aim to decrease the risk of including subjects with chronic obstructive pulmonary disease [COPD]); (c) were taking oral corticosteroid therapy; (d) had an asthma exacerbation four weeks before screening; (e) were unable to perform pulmonary function tests; or (f) had pulmonary disease other than asthma.

All subjects underwent baseline physical examinations including routine assessment of anthropometry and blood pressure and collection of blood samples. Waist circumference was measured directly to the body surface midway between the lower rib margin and the ileac crest. Fat free mass and fat weight (in kg and % body weight) were measured using bio-electrical impedance analysis (Bodystat 1500, Bodystat Ltd, British Isles).

Percentage excess weight loss (%EWL) was calculated as: (BMI baseline – BMI 12 months follow up) / (BMI baseline – 25) * 100.

Pulmonary function tests

Spirometry was performed with Vmax spirometer (Vmax SensorMedics Viasys, type Encore 20/22/229/62 Encore, Cardinal Health, USA) before and after 400 µg of inhaled salbutamol, according to the American Thoracic Society / European Respiratory Society guidelines[20, 21]. Static lung volumes were measured by body plethysmography, directly after the spirometry. If applicable, subjects were asked not to use longacting β2-agonists for 48 h, short-acting β2-agonists for 8 h and anti-histamines or anti-leukotriene medication 72 h before lung function testing. Subjects who were using inhaled corticosteroids (ICS), were asked to discontinue them until bariatric surgery. Daily symptom diary and daily peak flow rates were used to screen asthma control. Subjects were permitted to use short-acting bronchodilators as rescue medication. After six weeks they returned for their second visit, during which exhaled Nitric Oxide (Fe_{NO})(Niox mino Aerocrine, Sweden)[22], impulse oscillometry (IOS) (Masterscreen IOS system, Erich Jaeger Co., Würzburg, Germany), diffusion capacity (intrabreath method, corrected for hemoglobin and alveolar volume)[23] and methacholine provocation testing (five breath dosimeter method) [24, 25] were performed. Bronchial responsiveness to methacholine was expressed as the

provocative dose of methacholine inducing a 20% fall in FEV_1 (PD_{20}). A PD_{20} < 1.8 mg was considered as a positive provocation test. If the methacholine provocation test was negative, a second provocation test was performed six weeks later. If the methacholine provocation test was negative, a second provocation test was performed six weeks later. The use of ICS was allowed during follow up.

At 3 and 6 month follow-up FEV_1 was measured by methacholine provocation testing. At 12-month follow-up two visits were scheduled. During the first visit, spirometry and body plethysmography were performed. During the second visit, Fe_{NO}, IOS, diffusion capacity and methacholine provocation testing were performed.

Questionnaires and comorbidities

Based on questionnaires the subjects with asthma were grouped into child onset of asthma if they have had the diagnosis asthma before the age of 18, and adult onset of asthma from 18 years or older. Asthma symptoms were assessed by the mini Asthma Quality of Life Questionnaire (AQLQ)[26] and the Asthma Control Questionnaire (ACQ) [27] to assess asthma complaints. An delta of 0.5 in either AQLQ or ACQ was considered clinically significant. The Epworth Sleepiness Scale[28] questionnaire was used to assess OSAS, and the GERD-Questionnaire for gastro-esophageal reflux disease (GERD) [29]. The average of 7 days data collected with an activity meter was used to determine the total number of steps taken a day, as a measure of activity. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program's Adult Treatment Panel III report (NCEP ATP-III) criteria when ≥3 of the following 5 risk factors were present: abdominal obesity, an elevated level of serum triglycerides, low serum level of high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and high serum glucose level or treatment for any of these disorders[30].

Atopy

Atopy was defined as either a positive skin-prick test (SPT) or a positive serum inhalation screen. The skin-prick tests (SPT) consisted of a battery of common aeroallergens: house-dust mite; dog, cat, and horse dander; *Aspergillus fumigatus*; mugwort; and birch and grass pollen (Vivodiagnost; ALK Benelux BV, Groningen, The Netherlands). A positive SPT was defined as at least one reaction to the aforementioned allergens as compared to the histamine positive control and saline solution-negative control. Total IgE and specific serum IgE were determined with a solid-phase two-step chemiluminescent immunoassay on the Immulite 2000 (Siemens, Los Angeles, CA). A positive serum inhalation screen was defined as at least one increased amount of specific IgE for fungus, house-dust mite, cat, dog, grass, birch or herbs.

Laboratory

Laboratory measurements were performed according to standard procedures by our Department of Clinical Chemistry. Plasma-cholesterol, HDL-cholesterol, glucose, and triglycerides, were measured using LX-20 and DxC analyzers (Beckman Coulter, Miami, FL, USA). LDL-cholesterol was calculated using the Friedewald formula. Blood cell counts and 5-part leukocyte differentiation were determined automatically using LH750 or DxH800 analyzers (Beckman Coulter). Vitamin D was determined by radioimmunoassay or chemiluminescence (LIA) on Liason analyzers (DiaSorin, Stillwater, MN, USA). Serum markers of systemic inflammation were assessed using the Meso Scale Discovery Platform (Meso Scale Discovery, Gaitherburg, MD), for IL-6, IL-8, high-sensitivity (hs)-CRP, TNFα, GM-CSF, leptin and adiponectin. Lower limit or upper limit of detection were respectively 0.7-2500 pg/ml, 0.6-2500 pg/ml, 0.05-142 ng/ml, 0.8-2500 pg/ml, 0.61-2500 pg/ml, 0.2-100 ng/ml and 0.064-1000 ng/ml. All values which were below or above the lower or upper limit of detection of the assay, were arbitrarily set at these limits.

RESULTS

In the BS+A group median BMI decreased from 45.1 kg/m^2 to 35.9 kg/m^2 at 3-month follow-up, 33.0 kg/m^2 at 6-month follow-up and 30.2 kg/m^2 at 12-month follow-up ($p<0.001$ for all comparisons). In the BS-A group median BMI decreased from 43.1 kg/m^2 to 36.0 kg/m^2 at 3-month follow-up, 32.3 kg/m^2 at 6-month follow-up and 29.0 kg/m^2 at 12-months follow-up ($p<0.001$ for all comparisons). The BMI was stable in the NBS+A group (35.6 kg/m^2 at baseline, 35.3 kg/m^2 at 3-month follow-up, 35.6 kg/m^2 at 6-month follow-up and 36.2 kg/m^2 at 12-month follow-up).

Also the median abdominal circumference improved in the BS+A group (133 cm baseline, 99cm 12-month follow-up; $p<0.001$) as well as in the BS-A group (127 cm baseline, 93 cm 12-month follow-up; $p<0.001$), but not in the NBS+A group (119 cm baseline, 113 cm 12-month follow-up).

AQLQ improved clinically and statistically significantly at 12-month follow-up as compared to baseline for the BS+A group (median 5.6 to 6.7, $p= 0.002$), and BS-A group (median 6.3 to 6.9, $p<0.001$). There was no significant improvement in the NBS+A group (median 5.5 to 5.8, $p=0.075$). ACQ improved clinically and statistically significantly at 12-month follow-up as compared to baseline for BS+A group (median 1.2 to 0.4, $p= 0.001$), and the NBS+A group (1.7 to 1.0, $p= 0.012$), and only statistically significantly in the BS-A group (median 0.3 to 0.0, $p= 0.001$). While there was a significant difference between BS+A and BS-A group at baseline ($p=0.001$), there was no difference between these group at 12-month follow-up ($p=0.057$).

Table S1 B Demographics of the study population

	NBS+A	BS+A	BS-A	p Value
Bio-impedance				
Fat free Mass	56.3 (42.9-7-9)	61.2 (47.8-100.5)	62.0 (47.2-74.7)	0.103
Fat weight (%)	43.5 (24.5-59.5)	50.9 (37.6-70.4)	50.6 (31.1-59.1)	0.124
Fat weight (kg)	45.1 (27.6-79.0)	68.1 (44.5-134.4)	62.3 (32.0-100.0)	0.046
Asthma				
Medication use at inclusion study				
Short acting bronchodilator	35.7%	41.4%	25.0%	0.367
Long acting bronchodilator	14.3%	3.4%	2.3%	0.153
Antileukotrienes	35.7%	0%	2.3%	<0.001
B_2 sympaticomimetica/ ICS	71.4%	20.7%	6.8%	<0.001
Inhaled corticosteroids	21.4%	17.2%	6.8%	0.227
Antihistamines	23.1%	24.1%	13.6%	0.447
Nasal corticosteroids	71.4%	17.2%	11.4%	<0.001
Age of onset of asthma (% as child)	75%	33%		
Atopy				
Positive inhalation screen	Not done	69.2%	42.4%	0.049
Skin prick test (% ≥1 positive wheal)	78.6%	55.2%	31.8%	0.005
IgE (kU/L)	90.7 (5.8-2026.0)	213 (5.0-2329)	52 (1.4-761.0)	0.041
Comorbidities				
Epworth Sleepiness Scale	2 (0-16)	2 (0-8)	2 (0-9)	0.964
GERD-questionnaire	6 (4-12)	6 (4-12)	6 (2-14)	0.296
Steps a day	7191 (3307-9587)	4964 (2021-12176)	4613 (2061-10083)	0.155
Metabolic syndrome	27.3%	59.3%	53.8%	0.206
Laboratory[1]				
Cholesterol (mmol/L)	4.3 (2.9-5.8)	4.7 (3.4-7.4)	5.0 (3.0-6.9)	0.570
HDL-cholesterol (mmol/L)	1.1 (0.8-1.7)	1.1 (0.7-2.3)	1.2 (0.7-2.1)	0.725
LDL-cholesterol (mmol/L)	2.7 (1.0-3.6)	2.9 (1.8-5.1)	3.0 (1.6-4.8)	0.634
Triglyceride (mmol/L)	1.2 (0.8-2.4)	1.7 (0.6-3.3)	1.4 (0.5-5.1)	0.080
Glucose (mmol/L)	5.2 (4.2-9.4)	5.6 (4.6-9.5)	5.9 (4.0-27.1)	0.029
Peripheral blood count				
Leukocytes (10^9 /L)	9.2 (4.6-12.3)	8.7 (5.3-13.1)	7.2 (4.6-11.9)	0.057
Neutrophils (%)	59 (37-79)	61 (45-72)	59 (46-70)	0.144
Lymphocytes (%)	31 (15-48)	28 (15-45)	31 (20-47)	0.282
Monocytes (%)	7 (4-14)	7 (5-13)	6 (4-13)	0.837
Eosinophils (%)	2 (0-7)	2 (0-9)	2 (0-6)	0.965
Basophils (%)	0 (0-1)	0 (0-1)	0 (0-2)	0.814

Data are presented as median (min-max)

[1] non fasting blood

BS+A, bariatric surgery and asthma group; BS-A, bariatric surgery without asthma group; ICS, inhaled corticosteroid; NBS+A, no bariatric surgery and asthma group

Table S4 Submucosal cell counts of bronchial biopsies, before and 12 months after bariatric surgery

	BS+A			BS-A		
	Baseline	**12-month FU**	**p Value**	**Baseline**	**12-month FU**	**p Value**
Eosinophils (EG2)	3.0 (0.04-20.2)	1.4 (0.04-133.2)	0.889	1.3 (0.03-27.1)	2.5 (0.04-42.7)	0.826
Neutrophils (NE)	54 (11-273)	111 (24-361)	0.208	47 (0.1-139)	71 (3-228)	0.221
Mast cells (AA1)	118 (75-236)	61 (6-248)	0.036	152 (84-262)	145 (24-213)	0.125
Macrophages (CD68)	271 (67-520)	151 (65-373)	0.161	191 (7-531)	208 (58-569)	0.570
B cells (CD20)	28 (5-243)	45 (0.1-82)	1.000	36 (0.1-402)	26 (0.1-205)	0.570
T cells (CD8)	945 (321-2304)	566 (55-965)	0.050	1040 (0.2-2377)	493 (94-2641)	0.053
T cells (CD4)	510 (24-2393)	241 (6-1013)	0.161	434 (0.07-1136)	186 (0.04-719)	0.211
T cells (CD3)	1000 (161-3433)	732 (164-1165)	0.401	844 (459-2193)	559 (43-1753)	0.015

Bronchial submucosal cell count in morbidly obese subjects before and 12 months after bariatric surgery, with (BS+A, n=8) and without asthma (BS-A, n=14). p Values were calculated for the comparison between baseline and 12 months follow up within each group. Data are presented as the median (min-max), cells/ mm^2 submucosa.

PART D

SUMMARY

8

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

Obesity has historically been viewed as a sign of wealth and prosperity. However, obesity is not a medical disorder that started with the industrial revolution, since already Hippocrates wrote that "Corpulence is not only a disease itself, but the harbinger of others"[1]. The current epidemic of obesity has revealed various co-morbidities associated with obesity. Asthma is one these co-morbidities which are associated with obesity, and is the focus of the research described in the present thesis. The main topic of this thesis is whether the relationship between obesity and asthma is causal or that obesity and asthma are two co-incidental diseases in the same person.

Main findings

In **chapter 2** we have shown that both overdiagnosis as well as underdiagnosis of asthma occur in the morbidly obese. A diagnosis of asthma based on symptoms alone is unreliable in the morbidly obese, and pulmonary function testing is an essential part of the diagnosis of asthma in the morbidly obese[2].

As overdiagnosis of asthma cannot fully explain the interplay between obesity and asthma, we explored other explanations. In **chapter 3** all possible known explanations were discussed. As a new explanation the metabolic syndrome was suggested[3]. To investigate whether the metabolic syndrome might explain the relationship between obesity and asthma, we explored in **chapter 4** the relationship between airflow obstruction (FEV_1/FVC) – an essential component of the diagnosis of asthma – and the metabolic syndrome. This study showed a small, but statistically significant, difference in eosinophils and FEV_1/FVC between subjects with and without the metabolic syndrome[4]. After correction for other variables, an association between blood eosinophils and FEV_1/FVC remained. Although the differences we have found were relatively small, it might support our hypothesis that the presence of the metabolic syndrome may influence lung function impairment, through the induction of systemic inflammation, in particular, mediated by blood eosinophils.

We therefore investigated in **chapter 5** characteristics of bronchial biopsies from morbidly obese asthma patients and morbidly obese controls. We were surprised to find that despite evidence for systemic inflammation, which seemed to be related to the level of asthma control, there was no evidence for bronchial inflammation in the morbidly obese as shown e.g. by the absence of increased numbers of eosinophils or neutrophils[5].

Bariatric surgery is considered a definitive solution for morbid obesity, as weight loss is permanent in contrast to dieting, which is most often a temporary solution. In **chapter 6** we have shown that subjects with complications within 30 days of bariatric surgery more often have airflow reversibility or airflow obstruction[6]. Therefore, as symptoms indicative of airway disease are often unreliable in the morbidly obese – as already

discussed in chapter 2 - , pulmonary function tests should routinely be part of the preoperative risk assessment.

In **chapter 7** we extensively looked at both clinical, physiological, systemic and bronchial mucosal inflammatory parameters before and after bariatric surgery in morbidly obese asthma subjects and morbidly obese control subjects. Although we found no improvement in our primary endpoint FEV_1/FVC, we did find improvement in asthma control, quality of life, medication use and PD_{20} methacholine. The significant improvement of R_5-R_{20} (peripheral airway function) after bariatric surgery, which was associated with BMI, ACQ and PD_{20}, suggests that peripheral airways play a major role in the relationship between obesity and asthma. Finally, bariatric surgery also decreased markers of systemic inflammation, and mast cell counts in bronchial submucosa of obese asthma subjects. Collectively these findings emphasize that weight loss as achieved by bariatric surgery should be a cornerstone in the treatment of morbidly obese asthma patients.

Based on my main findings, this discussion is subdivided into three main topics. First, I will discuss the pitfalls concerning the diagnosis of asthma, especially in the morbidly obese. Then, I will describe bronchial and systemic inflammation in the morbidly obese. Thereafter I will address bariatric surgery in the morbidly obese, and will especially focus on the therapeutic effect of bariatric surgery in morbidly obese asthma patients.

Diagnosis of asthma in the morbidly obese

The first step to investigate the possible causal relationship between asthma and obesity, is to be sure that the diagnosis of asthma is correct. According to the latest Global Initiative for Asthma (GINA) definition of 2014, asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation[7]. Although the GINA guidelines are clear in stating that besides symptoms, also objective measurements of variable expiratory airflow limitation are necessary for the diagnosis of asthma - implying that lung function testing is mandatory for the diagnosis of asthma - in daily practice the diagnosis of asthma is often made only on the basis of symptoms[8]. Especially within the morbidly obese population, this symptom-based approach has been proven to be of limited value. Morbidly obese do often have dyspnea and the diagnostic challenge is to distinguish dyspnea resulting from overweight and dyspnea due to asthma. In **chapter 2** we have shown that both overdiagnosis as well as underdiagnosis of asthma occur in the morbidly obese. A diagnosis of asthma based on symptoms alone is unreliable in the morbidly obese patient population, and pulmonary function testing is an essential part in the diagnostic progress of asthma in the morbidly obese[2].

To our knowledge, this is the first study that not only focuses on overdiagnosis but also on underdiagnosis of asthma in this patient population. Underdiagnosis of asthma can lead to undertreatment, increased morbidity and eventually possible death. On the other hand, overdiagnosis leads to overtreatment with possible risk of side-effects of the inhaled corticosteroids and high health costs. It can be argued that the use of inhaled corticosteroids (ICS) can influence the results of the provocation test[9], however stopping of ICS use is a possibility to correct for this. Many clinicians are reluctant to do this, but we have shown that it can be done in most morbidly obese (asthmatic) patients without complications (ref; unpublished observations).

Many of the population-based studies use a physician-diagnosis of asthma. The question thus arises, whether this physician diagnosis of asthma is correct, especially in the morbidly obese. However, as a result of the inclusion method of our study in chapter 2, we cannot make any statement on the frequency of underdiagnosis or overdiagnosis in the total morbidly obese population. So, it is still unclear whether overdiagnosis of asthma truly explains the relationship between obesity and asthma. Further research in a cross-sectional study in the general population in which *all* subjects undergo spirometry and bronchial provocation testing could answer this question.

Bronchial and systemic inflammation in the morbidly obese

As overdiagnosis of asthma cannot fully explain the interplay between obesity and asthma, we explored other explanations. In **chapter 3** all possible known explanations are discussed.

"Obese asthma" may be a unique phenotype of asthma, characterized by decreased lung volumes, greater symptoms for a given degree of lung function impairment, destabilization or lack of asthma control, lack of eosinophilic inflammation and a different response to controller medication. Therefore, the clinical evaluation of an obese patient with asthma must require a more rigorous and objective approach. Whether this relationship is really causal or represents parallel co-morbidities is unclear. In animal models, there is an increasing amount of evidence for the role of adipokines derived from fat tissue in the relationship between obesity and asthma. These adipokines cause a low grade systemic inflammation, which might cause or enhance bronchial inflammation. The data are conflicting in humans. However, the fact that weight loss improves asthma control and normalizes the concentration of adipokines in the circulation implies that there must be some role for adipokines in the relationship between obesity and asthma.

A hypothesis not discussed in chapter 3, is the effect of gut microbiota on asthma and obesity. The modern dietary pattern with reduced fiber content is associated with changes in gut microbiota biodiversity, which is a risk factor for allergy and obesity[10]. The gut microbiota and the microbiome (collective genetic material of gut microbiota) are important in normal immune development. A disruption of the gut microbiota

increases immune and metabolic dysregulation, and increases the risk of obesity and asthma. The changing gut microbiota is linked to inflammation through increased CRP, TNFα and IL-6[11]. The hygiene hypothesis states that excessive cleaning and reduced pathogen exposure contribute to inadequate immune responses[12]. A link can be seen with the gut microbiota which can be influenced by diet and antibiotics use, and some state that the hygiene theory should be rewritten into the "microflora hypothesis"[13]. This hypothesis postulated that disturbances in gut microbiota lead to underdeveloped microbiota, which impair proper maturation of the immune system leading to allergic hypersensivity and asthma. But also obesity is influenced by altered gut microbiota. In obese subjects the gut barrier is altered leading to higher plasma lipopolysaccharide levels which trigger low grade inflammation and insulin resistance[14]. Because the notion that gut microbiota affects obesity and asthma is a recent insight, we have not performed any research on this subject yet.

Another explanation how obesity can influence asthma is the metabolic syndrome (mentioned in chapter 3). Since obesity is a component of the metabolic syndrome and the metabolic syndrome also includes systemic inflammation, it is to be expected that there is a relationship between metabolic syndrome and asthma. The few data that are available show that there is no relationship between metabolic syndrome and asthma, but there is one between the metabolic syndrome and asthma-like symptoms.

To investigate whether the metabolic syndrome might explain the relationship between obesity and asthma, we explored in **chapter 4** the relationship between airflow obstruction (FEV_1/FVC) – an essential component of the diagnosis of asthma – and the metabolic syndrome. This study showed a small, but statistically significant, difference in eosinophils and FEV_1/FVC between subjects with and without the metabolic syndrome[4]. After correction for other variables, an association between blood eosinophils and FEV_1/FVC remained. Although the differences we have found were relatively small, it might support our hypothesis that the presence of the metabolic syndrome may influence lung function impairment, through the induction of systemic inflammation, in particular, mediated by blood eosinophils.

Insulin resistance, another part of the metabolic syndrome, might also help to explain the relationship between obesity and asthma. Hyperinsulinemia may lead to changes in the lung characteristics of asthma via growth factor-like effects[15]. A vagally mediated bronchoconstrictor effect of hyperinsulinemia has also been described[16]. A study in healthy adults has found an association between insulin resistance and bronchial hyperresponsiveness[17]. We however, found that only hypertension – as one of the five components of the metabolic syndrome – was associated with FEV_1/FVC and furthermore, we did not test bronchial hyperresponsiveness.

After we had found more circumstantial evidence that systemic inflammation might explain the relationship between asthma and obesity, we investigated whether this systemic inflammation also leads to local bronchial inflammation. As bronchial inflammation is considered a key component of asthma, if bronchial inflammation in present in the morbidly obese asthma subject, it would argue for a causal relationship between obesity and asthma.

Whereas other studies tried to investigate this bronchial inflammation by bronchial lavage or bronchial brushes, it can be argued whether they truly investigated bronchial inflammation. There might be a difference in the inflammatory cell population within the airway epithelium (as investigated by lavage, brushes or bronchial biopsies) and that in submucosa (as investigated by bronchial biopsies). We therefore investigated in **chapter 5** characteristics of bronchial biopsies from morbidly obese asthma patients and morbidly obese controls.

As we found in chapter 4 that increased numbers or circulating eosinophils could be a specific manifestation of the systemic inflammation associated with the metabolic syndrome, it could be expected that asthma in the morbidly obese is also an eosinophil driven disease as it is known to be in many lean atopic asthma subjects. However, there is large debate in literature about the nature of the inflammation in obese asthma subjects. Asthma in the obese has been characterized as a specific phenotype, with a female predominance, late on-set and not eosinophilic[18].

We were surprised to find that despite evidence for systemic inflammation, which seemed to be related to the level of asthma control, there was no evidence for bronchial inflammation in the morbidly obese, characterized by increased numbers of eosinophils or neutrophils[5]. Despite one part of the morbidly obese study population was diagnosed as having asthma, while the other part of the morbidly obese study population had no asthma, there was no difference in any of the components of bronchial inflammation studies with the exception of CD8 positive T-cells. Both groups had the same degree of obesity, had no differences in lung function, or prevalence of the metabolic syndrome. A good explanation why one group has asthma and the other not, despite the fact that there is no difference in bronchial inflammation remains a question to be elucidated.

Our data suggest that asthma in our cohort is not driven by a classical T_H2-mediated mechanism and probably needs to be regarded as a distinct phenotype of the disease, not related to significant detectable inflammatory responses in the airway walls. Possibly asthma in the *morbidly obese* – as were the subjects of our studies – constitutes a specific phenotype, which is distinct from asthma in *obese* subjects. Desai *et al.*[19], who investigated obese asthma subjects (mean BMI 36 kg/m^2 versus mean BMI 44 kg/m^2 in our study), did find an elevated bronchial submucosal eosinophil number as compared to lean controls and lean asthmatics. Others discuss that the lack of airway eosinophils could be altered trafficking of these cells from the vasculature or interstitium into the

airspace rather than a unique inflammatory phenotype per se[20]. While others state that the location of the eosinophils within specific tissues may directly affect their function[21]. Additionally, we also found no evidence for neutrophil-dominated bronchial inflammation, as has been shown in an obese asthma group by Scott[22].

Furthermore our study was the first to compare bronchial biopsies from morbidly obese asthma subjects to morbidly obese controls. Previous studies compared obese asthmatics with lean asthmatics, and found differences. It should be kept in mind that these differences can also be attributed to obesity rather than asthma.

As the classical Th2-mediated mechanism seems not to be present in the morbidly obese with asthma, other mechanisms could be active. Another cell type of interest are the macrophages. Blood monocytes and adipose tissue macrophages in obesity demonstrate a classical M1 activation. Lugogo *et al* compared macrophages of 42 obese subjects with asthma with 46 obese subjects without asthma, and found that alveolar macrophages in obese asthmatics demonstrate an exaggerated response to the proinflammatory effect of leptin[23]. Furthermore, Fernandez has showed that in obese asthmatics the efferocytosis (the process by which macrophages ingest and clear apoptotic cells) of blood monocytes and airway macrophages in obese asthmatics was 40% lower as compared to lean asthmatics. Although we found no differences in the number of macrophages in the bronchial tissue between morbidly obese asthmatics and morbidly obese controls, of course there could have been a difference in macrophage function. Further research should also focus on macrophages in the fat tissue, and whether these macrophages in the fat tissue also influence systemic inflammation and thereby bronchial inflammation.

T_H17 cells, developmentally distinct from T_H1 and T_H2 cells, could also play a role in the relationship between obesity and asthma, as IL-17A – produced by T_H17 cells, but also by other cell types - is required for the development of bronchial hyperresponsiveness in obese mice[24]. Furthermore, Mathews *et al.* have recently shown that the increases in IL-17A precedes the development of bronchial hyperresponsiveness by several weeks in mice[25], suggesting that obesity and asthma are not two co-incidental diseases. Data on IL-17A in obese humans with asthma is rare, and it also was not a subject of our research.

Air pollution is now mentioned as a novel risk factor for the development of obesity[26] and asthma, and research is now focusing on bronchial inflammation caused by air pollution[27]. Endocrine-disrupting chemical (EDC) are chemicals that can disrupt adipogenesis and energy balance. Air pollution can induce obesity via a systemic inflammatory pathway that targets adipocytes[28]. Many EDCs are highly lipophilic and therefore accumulate in the fat tissue, where they can release proinflammatory signals but also may cause adipocyte proliferation and differentiation. This seems quite plausible, and might explain the exploding prevalence of obesity in the last decades, other than excess caloric intake, sedentary lifestyle or genetic susceptibility. However, it is now also stated

that obese individuals are more vulnerable to develop asthma due to exposure to air pollutants than lean individuals. In a study with 148 children with persistent asthma, the association between indoor particulate matter less than 2.5 µm in mean aerodynamic diameter ($PM_{2.5}$) and nitrogen dioxide (NO_2) levels and respiratory symptoms were examined. Overweight children were more susceptible to pulmonary effects of $PM_{2.5}$ and NO_2[29]. This does not answer whether it is asthma or obesity that made the children more susceptible to EDCs. In a mouse study by Shore *et al*, obese mice inhaled greater doses of air pollutant ozone in the lungs than normal weight mice because of higher breathing frequency, accompanied by greater airway hyperresponsiveness and greater cellular inflammation[27]. This is not in line with our results of bronchial tissue inflammation, as discussed in **chapter 5**, where we found no difference in cellular inflammation between obese subjects with or without asthma. This might be explained by the fact that there might be an association between air pollutants and asthma or obesity, but this is not a causal relationship. Further research on air pollution is needed.

Since we found no difference in bronchial inflammation between obese asthma subjects and obese controls, it can be argued that the definition of asthma as a syndrome characterized by airway hyper-responsiveness, inflammation and clinical symptoms, as presented in the GINA guidelines, is perhaps not applicable to the morbidly obese. In the present study, all asthma subjects had symptoms, reversible airway obstruction or increased bronchial hyper-reactivity. In contrast, in majority of patients no airway inflammation could be detected. This further strengthens the concept of a different asthma phenotype, whereas the phenotype observed in the present study has no distinct inflammatory changes in the airways. This phenomenon probably explains why these patients have such a poor response to anti-inflammatory medication. Weight loss seems to be the most important therapeutic goal, although further research on this subject is needed.

Bariatric surgery

Bariatric surgery is considered a definitive solution for morbidly obesity. In line with the worldwide epidemic of obesity, the number of bariatric surgery procedures being performed is increasing every year, with a 22-fold increase between 1996 en 2008[30]. The prevention of complications of bariatric surgery is of great importance, especially since surgery is elective and complications are difficult to treat in this group of morbidly obese patients. As we have shown in chapter 4 that morbidly obese subjects with the metabolic syndrome have a slight, but statistically significant, increase in airflow obstruction, we wondered whether subjects with more airflow obstruction or airflow reversibility, had more complications after bariatric surgery. In **chapter 6** we have shown that subjects with complications within 30 days of bariatric surgery more often have airflow reversibility or airflow obstruction[6]. Therefore, as symptoms are often unreliable

in the morbidly obese – as already discussed in chapter 2 - , pulmonary function tests should routinely be part of the preoperative risk assessment. Generally, laparoscopic bariatric surgery is safe, but randomized prospective studies are needed to investigate whether abnormal pulmonary functions tests could indeed serve as a guide in patient selection and optimization of the preoperative medical condition of patients undergoing bariatric surgery, which could lead to additional improvement in the outcomes after bariatric surgery.

The current guidelines of the American Society of Metabolic and Bariatric Surgery state that spirometry as a preoperative test is indicated only in the presence of risk factors previously identified by other tests[31]. A recent study by Clavellina *et al* in 602 patients, which investigated the relationship between spirometry results and the frequency of postoperative complications[32], supports our study results. They also found that using multivariate logistic regression analysis, an abnormal spirometry was a significant predictor of post-operative pulmonary complications in patients with respiratory symptoms and/ or obstructive sleep apnea syndrome (OSAS). However, they state that there was a significant number of asymptomatic patients that in spite of an abnormal spirometry, did not develop respiratory complications[32], and therefore argue that spirometry should not be performed regularly before bariatric surgery. A large study of 158405 patients in the USA, which focused on pulmonary complications of bariatric surgery, found that not only the metabolic syndrome, but also asthma is a risk factor for postoperative pulmonary complications[33]. However, as discussed previously, the major pitfall of this article was that the asthma diagnosis was based on physician assessment and no spirometry was performed. As the metabolic syndrome is seen as a state of systemic inflammation, it is logical to speculate that subjects with (more) systemic inflammation have a higher change of complications of bariatric surgery. The abovementioned US study found that the metabolic syndrome is associated with complications of bariatric surgery, we although did not find such an association.

Interestingly, our study has shown that spirometry is not only useful in predicting pulmonary complications, but it might predict all complications of bariatric surgery. This it is in line with previous findings that FEV_1 is associated with mortality[34]. FEV_1 could possibly be a marker of general health or fitness. So abnormal spirometry does not only indicate obstructive pulmonary disease, but might also indicate poor general health. In this cohort we had no data on systemic or bronchial inflammation. It is purely speculative to say that the group with abnormal spirometry also had more systemic inflammation.

Only a randomized controlled intervention study which investigates whether therapy in subjects with abnormal spirometry could prevent complications of bariatric surgery, could answer whether spirometry should be standard in all bariatric subjects. Such a study has not yet been performed to our knowledge.

After showing in chapter 5 that bronchial inflammation is absent in the morbidly obese, in contrast to systemic inflammation, we further explored the effects of weight loss by bariatric surgery. In **chapter 7** we extensively looked at both clinical, physiological, systemic and bronchial musical inflammatory parameters before and after bariatric surgery in morbidly obese asthma subjects and morbidly obese control subjects[35]. Although we found no improvement in our primary endpoint FEV_1/FVC, we did find improvement in asthma control, quality of life, medication use and PD_{20} methacholine. The significant improvement of R_5-R_{20} (peripheral airway function) after bariatric surgery, which was associated with BMI, ACQ and PD_{20}, suggests that peripheral airways play a major role in the relationship between obesity and asthma. Finally, bariatric surgery also decreased markers of systemic inflammation, and mast cell counts in bronchial submucosa of obese asthma subjects.

The fact that we did not find clear evidence that also bronchial inflammation is decreased concordantly with the systemic inflammation, is in contrast to the results of Arismendi *et al*[36]. They showed not only that in a group of healthy obese subjects, systemic inflammation is not modified by sex, smoking status or metabolic syndrome, but also that pulmonary inflammation, as measured by exhaled IL-8, IL-10 and 8-isoprostane, is increased in obese healthy subjects as compared to lean healthy subjects, and furthermore that this pulmonary inflammation in decreased after bariatric surgery. However, they did not include subjects with asthma. And as stated previously, the question remains whether there are cellular differences with regard to inflammation between the submucosa and the epithelium.

Obesity is associated with increased oxidative stress. Exhaled 8-isoprostane, derived from free radical-catelyzed peroxidation of arachidonic acid, is a marker of oxidative stress. Oxidative stress is characterized by the presence of increased reactive oxygen species (ROS). ROS production contributes to increased mucus production and increased airway reactivity. Increased plasma 8-isoprostane levels have been noted in asthma, but were not present after adjusting for obesity[37]. This suggests that the elevated plasma levels are a consequence of obesity rather than asthma.

Recently there is more recognition that bioenergetic failure is a common pathway rather than a outcome of disease, in obesity, metabolic syndrome and asthma[38, 39]. Mitochondrial dysfunction seems to be related to the metabolic syndrome. Surplus nutrient supply overloads mitochondria[40], leading to overproduction of (ROS) and accumulation of incompletely oxidized substrates. The damage of these ROS causes reduction in mitochondrial integrity, and triggers stress pathways that reduce insulin sensitivity[41]. Together with the sedentary lifestyle, this appears to be the foundation of insulin resistance. As fatty acid oxidation for energy can only happen in mitochondria, fats are not adequately metabolized, leading to intracellular accumulation and increased circulating lipids[41]. This is the trias of obesity, hyperglycaemia and dyslipidemia, also known as the

metabolic syndrome. As hypersinsulinemia seems to be an independent risk factor for asthma[15], mitochondrial mechanisms important in the metabolic syndrome can also contribute to asthma. Although in mice models of allergic airway inflammation, mitochondrial dysfunction has been demonstrated[41], there is limited evidence for a causal role of mitochondrial dysfunction in human asthma. The exact role of oxidative stress in the relationship between asthma and obesity has yet to be elucidated, and should be focus of further research.

As previously discussed, we take the view that morbidly obese asthmatics are a distinct phenotype on its own, in contrast to obese asthmatics. It is also speculated that the obese asthma phenotype could be further divided into Th2-high (high serum IgE) obese asthmatics having pre-existing allergic asthma that is complicated by obesity, whereas Th2-low (low serum IgE) obese asthmatics develop asthma symptoms as a consequence of obesity. This subphenotyping is confirmed by the fact that airway hyperresponsiveness in Th2-low obese asthmatics improves after weight loss following bariatric surgery, in contrast to Th2-high obese asthmatics[42].

Traditionally asthma research has focused on the large airways. However, small airways are also an important site of airway inflammation and remodeling in asthma[43]. There are only a few studies on small airways in (lean) asthma[44, 45], the list of small airway studies in subjects with obesity is even smaller[46]. With impulse oscillometry (IOS) the resistance and reactance of the airways can be measured easily. Resistance at 20Hz is considered to reflect the large airways (R_{20}) and resistance at 5Hz the total airways (R_5). Small airway resistance can be calculated with the difference R_5-R_{20}. Reactance of the system at 5Hz (X_5) is also assumed to reflect small airway function[47]. Asthma symptoms correlate poorly with FEV_1, and in a recent study by Van der Wiel *et al*[44], which also included some obese subjects, it was shown that also small airway dysfunction poorly associated with asthma symptoms. However, they showed that small airway dysfunction is associated with more severe bronchial hyperresponsivenss to methacholine.

As small airways are now subject of current research in obese asthmatics, Chapman *et al*. investigated the effect of bariatric surgery on small airways and the two phenotypes of obese asthma, and found that weight loss does not alter small airway responsiveness inT_H2-high obese asthmatics, in contrast to T_H2 low obese asthmatics where weight loss is associated with a reduction in small airway responsiveness[46]. However, the patient numbers in this study are small (T_H2-low, n=8; T_H2-high, n=5). As our numbers are larger, this could explain why we did not find differences in subjects with either high or low IgE.

Treatment of (morbidly) obese asthmatics has proven to be difficult, as they respond poorly to conventional asthma therapies such as inhaled corticosteroids (ICS)[48]. As the conventional asthma therapies do not work, other researchers have investigated alternative options such as the effect of dietary weight loss[49-52]. The study by Stenius *et*

al.[49] showed that a 14-week weight reduction program using a low calorie diet leads to sustained improvement in lung function and health status. The role of exercise as intervention has not been studied extensively, although exercise or pulmonary rehabilitation could be of use especially in the morbidly obese asthma patient. However, it is difficult to obtain sustained weight loss in the morbidly obese with calorie restriction and behavioral interventions. Bariatric surgery causes a larger and prolonged effect on weight loss. Previous studies have also shown that bariatric surgery improves asthma control and airway hyperresponsiveness[53]. Some, however, state that the surgical technique is of influence on asthma related outcomes. A study of 257 patients with asthma showed after 1-year an overall reduction in asthma medication in all patients. Those who underwent a laparoscopic gastric banding procedure were 37% more likely to show improvement in self-reported asthma severity compared to those operated with the Roux-and-Y procedure[54]. Gastric banding is however a procedure that has become less common, due to complications, and is not performed in the Sint Franciscus Gasthuis. As far as we know there are no studies comparing the effects on medication use between gastric sleeve resection and gastric Roux-and-Y bypass. In addition, bariatric surgery does not only influence asthma, it also improves asthma comorbidities such as gastroesophageal reflux disease (GERD) and obstructive sleep apnea.

Other treatment options discussed in literature of obese asthma patients could be the use of either metformin or statins. Metformin restores insulin sensitivity and promotes mitochondrial metabolism[55]. In mice with diet-induced obesity, metformin attenuated allergen-induced eosinophilic inflammation[56]. The beneficial effects of metformin were not found in a genetically obese mice model with intrinsic airway hyperresponsiveness[57]. There is little data on the effect of metformin in human (obese) subjects with asthma. Further research is needed.

Statins which are classically prescribed for hyperlipidemia, have also found to have anti-inflammatory effect, and improve lung function[58]. In a retrospective study of 165 adult asthmatics it was found that patients on statins had significantly increased ACT scores as compared to those without statins[59]. However, medication related interventions were not part of our study.

All these findings together are underlining the importance of substantial weight reduction, in particular by bariatric surgery, which should be a cornerstone in the treatment of morbidly obese asthma patients. Furthermore, I would like to advocate that asthma should also be considered as one of the comorbidities – just like diabetes and OSAS – that makes patients eligible for bariatric surgery from a BMI level of 35 kg/m^2. Perhaps in future, morbidly obese asthmatic subjects will be sent more often to the surgeon, in addition to being sent to the pulmonologist, as "the surgeon can cure asthma in the morbidly obese".

FINAL REMARKS

The studies performed in this thesis illustrate the complicated interplay between obesity and asthma. With the results of our studies and recent findings reported in literature, figure 2 from the introduction could be altered into:

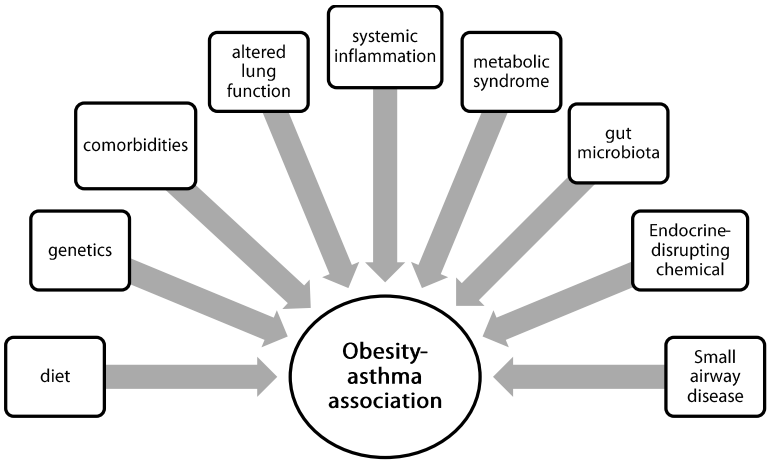

Figure 1 Hypothesis explaining the obesity-asthma association

The studies from this thesis show the complexity of relation and interaction between obesity and asthma. The observed epidemiological relationship between obesity and asthma does not prove causality, and cannot be completely explained by overdiagnosis of asthma, especially because also underdiagnosis of asthma exists within the obese population. The fact that in this population of morbidly obese we found an association between airway obstruction and eosinophils in the peripheral blood, particularly in those patients with the metabolic syndrome, indicates a possible causal relationship between obesity and asthma. However, this was contradicted by the fact that we found no difference in bronchial inflammation, including eosinophils between morbid obese patients with and without asthma. Despite evidence for more systemic inflammation, analysis of bronchial biopsies did not provide further clues for a pathophysiological basis of the interaction between obesity and asthma. Besides the clear need for a rigorous diagnosis of asthma in the morbidly obese, the question arises whether asthma in the *morbidly* obese is a distinct phenotype characterized by the absence of eosinophilic or neutrophilic inflammation. However, despite the absence of bronchial inflammation, substantial weight loss induced by bariatric surgery does improve lung function, quality of life and systemic inflammation in as both morbidly obese asthma patients as morbidly obese controls. This indicates that weight loss is the cornerstone for treatment of

the morbidly obese asthma phenotype, and that this observation may provide further clues for understanding the relationship between obesity and asthma.

Further research is necessary to show whether the abovementioned effects of bariatric surgery are also present after long term follow-up. Also research regarding the role of small airways in the morbidly obese asthma subject is necessary. Finally, the effect of pulmonary rehabilitation before bariatric surgery is an interesting topic for further research, and might reveal whether it decreases complications of bariatric surgery, and whether pulmonary rehabilitation on its own has any effect in the (morbidly) obese asthma patient.

Taken together, despite the fact that further research, especially directed at the role of the small airways, is necessary, I take the view that there is a causal relationship between obesity and asthma.

REFERENCES

1. Haslam DW, James WP. Obesity. *Lancet* 2005;366(9492):1197-209.
2. van Huisstede A, Castro Cabezas M, van de Geijn GJ, Mannaerts GH, Njo TL, Taube C, Hiemstra PS, Braunstahl GJ. Underdiagnosis and overdiagnosis of asthma in the morbidly obese. *Respir Med* 2013;107(9):1356-64.
3. van Huisstede A, Braunstahl GJ. Obesity and asthma: co-morbidity or causal relationship? *Monaldi Arch Chest Dis* 2011;73(3):116-23.
4. van Huisstede A, Cabezas MC, Birnie E, van de Geijn GJ, Rudolphus A, Mannaerts G, Njo TL, Hiemstra PS, Braunstahl GJ. Systemic inflammation and lung function impairment in morbidly obese subjects with the metabolic syndrome. *J Obes* 2013;2013:131349.
5. van Huisstede A, Rudolphus A, van Schadewijk A, Cabezas MC, Mannaerts GH, Taube C, Hiemstra PS, Braunstahl GJ. Bronchial and systemic inflammation in morbidly obese subjects with asthma: a biopsy study. *Am J Respir Crit Care Med* 2014;190(8):951-4.
6. van Huisstede A, Biter LU, Luitwieler R, Castro Cabezas M, Mannaerts G, Birnie E, Taube C, Hiemstra PS, Braunstahl GJ. Pulmonary function testing and complications of laparoscopic bariatric surgery. *Obes Surg* 2013;23(10):1596-603.
7. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014. *Available from: http://www.ginasthma.org/.* 2014.
8. Lucas AE, Smeenk FW, Smeele IJ, van Schayck CP. Overtreatment with inhaled corticosteroids and diagnostic problems in primary care patients, an exploratory study. *Fam Pract* 2008;25(2):86-91.
9. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990;142(4):832-6.
10. Marsland BJ. Influences of the microbiome on the early origins of allergic asthma. *Ann Am Thorac Soc* 2013;10 Suppl:S165-9.
11. Palmer DJ, Huang RC, Craig JM, Prescott SL. Nutritional Influences on Epigenetic Programming: Asthma, Allergy, and Obesity. *Immunol Allergy Clin North Am* 2014;34(4):825-837.
12. von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nat Rev Immunol* 2010;10(12):861-8.
13. Noverr MC, Huffnagle GB. The 'microflora hypothesis' of allergic diseases. *Clin Exp Allergy* 2005; 35(12):1511-20.
14. Ferreira CM, Vieira AT, Vinolo MA, Oliveira FA, Curi R, Martins FD. The Central Role of the Gut Microbiota in Chronic Inflammatory Diseases. *J Immunol Res* 2014;2014:689492.
15. Singh S, Prakash YS, Linneberg A, Agrawal A. Insulin and the lung: connecting asthma and metabolic syndrome. *J Allergy (Cairo)* 2013;2013:627384.
16. Nie Z, Jacoby DB, Fryer AD. Hyperinsulinemia potentiates airway responsiveness to parasympathetic nerve stimulation in obese rats. *Am J Respir Cell Mol Biol* 2014;51(2):251-61.
17. Kim KM, Kim SS, Lee SH, Song WJ, Chang YS, Min KU, Cho SH. Association of insulin resistance with bronchial hyperreactivity. *Asia Pac Allergy* 2014;4(2):99-105.
18. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178(3):218-24.
19. Desai D, Newby C, Symon FA, Haldar P, Shah S, Gupta S, Bafadhel M, Singapuri A, Siddiqui S, Woods J, Herath A, Anderson IK, Bradding P, Green R, Kulkarni N, Pavord I, Marshall RP, Sousa AR, May RD, Wardlaw AJ, Brightling CE. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. *Am J Respir Crit Care Med* 2013;188(6):657-63.

20. Sutherland ER. Linking obesity and asthma. *Ann N Y Acad Sci* 2014;1311:31-41.
21. Lloyd CM, Saglani S. Eosinophils in the spotlight: Finding the link between obesity and asthma. *Nat Med* 2013;19(8):976-7.
22. Scott HA, Gibson PG, Garg ML, Wood LG. Airway Inflammation is Augmented by Obesity and Fatty Acids in Asthma. *Eur Respir J* 2011;38(3):594-602.
23. Lugogo NL, Hollingsworth JW, Howell DL, Que LG, Francisco D, Church TD, Potts-Kant EN, Ingram JL, Wang Y, Jung SH, Kraft M. Alveolar macrophages from overweight/obese subjects with asthma demonstrate a proinflammatory phenotype. *Am J Respir Crit Care Med* 2012;186(5):404-11.
24. Kim HY, Lee HJ, Chang YJ, Pichavant M, Shore SA, Fitzgerald KA, Iwakura Y, Israel E, Bolger K, Faul J, DeKruyff RH, Umetsu DT. Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. *Nat Med* 2014;20(1):54-61.
25. Mathews JA, Wurmbrand AP, Ribeiro L, Neto FL, Shore SA. Induction of IL-17A Precedes Development of Airway Hyperresponsiveness during Diet-Induced Obesity and Correlates with Complement Factor D. *Front Immunol* 2014;5:440.
26. Limaye S, Salvi S. Obesity and Asthma: The Role of Environmental Pollutants. *Immunol Allergy Clin North Am* 2014;34(4):839-855.
27. Shore SA, Rivera-Sanchez YM, Schwartzman IN, Johnston RA. Responses to ozone are increased in obese mice. *J Appl Physiol (1985)* 2003;95(3):938-45.
28. Xu Z, Xu X, Zhong M, Hotchkiss IP, Lewandowski RP, Wagner JG, Bramble LA, Yang Y, Wang A, Harkema JR, Lippmann M, Rajagopalan S, Chen LC, Sun Q. Ambient particulate air pollution induces oxidative stress and alterations of mitochondria and gene expression in brown and white adipose tissues. *Part Fibre Toxicol* 2011;8:20.
29. Lu KD, Breysse PN, Diette GB, Curtin-Brosnan J, Aloe C, Williams DL, Peng RD, McCormack MC, Matsui EC. Being overweight increases susceptibility to indoor pollutants among urban children with asthma. *J Allergy Clin Immunol* 2013;131(4):1017-23, 1023 e1-3.
30. Buchwald H, Oien DM. Metabolic/bariatric surgery Worldwide 2008. *Obes Surg* 2009;19(12):1605-11.
31. Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, Heinberg LJ, Kushner R, Adams TD, Shikora S, Dixon JB, Brethauer S. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Endocr Pract* 2013;19(2):337-72.
32. Clavellina-Gaytan D, Velazquez-Fernandez D, Del-Villar E, Dominguez-Cherit G, Sanchez H, Mosti M, Herrera MF. Evaluation of Spirometric Testing as a Routine Preoperative Assessment in Patients Undergoing Bariatric Surgery. *Obes Surg* 2014.
33. Schumann R, Shikora SA, Sigl JC, Kelley SD. Association of metabolic syndrome and surgical factors with pulmonary adverse events, and longitudinal mortality in bariatric surgery. *Br J Anaesth* 2014.
34. Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* 2005;127(6):1952-9.
35. van Huisstede A, Rudolphus A, Castro Cabezas M, Biter LU, van de Geijn GJ, Taube C, Hiemstra PS, Braunstahl GJ. Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma. *Thorax* 2015;70(7):659-67
36. Arismendi E, Rivas E, Agusti A, Rios J, Barreiro E, Vidal J, Rodriguez-Roisin R. The Systemic Inflammome of Severe Obesity before and after Bariatric Surgery. *PLoS One* 2014;9(9):e107859.

37. Sood A, Qualls C, Arynchyn A, Beckett WS, Gross MD, Steffes MW, Smith LJ, Holvoet P, Thyagarajan B, Jacobs DR, Jr. Obesity-asthma association: is it explained by systemic oxidant stress? *Chest* 2009;136(4):1055-62.
38. Aravamudan B, Thompson MA, Pabelick CM, Prakash YS. Mitochondria in lung diseases. *Expert Rev Respir Med* 2013;7(6):631-46.
39. Mabalirajan U, Ghosh B. Mitochondrial dysfunction in metabolic syndrome and asthma. *J Allergy (Cairo)* 2013;2013:340476.
40. Cheng Z, Almeida FA. Mitochondrial alteration in type 2 diabetes and obesity: an epigenetic link. *Cell Cycle* 2014;13(6):890-7.
41. Agrawal A, Prakash YS. Obesity, Metabolic Syndrome, and Airway Disease: A Bioenergetic Problem? *Immunol Allergy Clin North Am* 2014;34(4):785-796.
42. Dixon AE, Pratley RE, Forgione PM, Kaminsky DA, Whittaker-Leclair LA, Griffes LA, Garudathri J, Raymond D, Poynter ME, Bunn JY, Irvin CG. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011;128(3):508-15 e1-2.
43. Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, Hogg JC. Inflammation of small airways in asthma. *J Allergy Clin Immunol* 1997;100(1):44-51.
44. van der Wiel E, Postma DS, van der Molen T, Schiphof-Godart L, Ten Hacken NH, van den Berge M. Effects of small airway dysfunction on the clinical expression of asthma: a focus on asthma symptoms and bronchial hyper-responsiveness. *Allergy* 2014.
45. van der Wiel E, ten Hacken NH, Postma DS, van den Berge M. Small-airways dysfunction associates with respiratory symptoms and clinical features of asthma: a systematic review. *J Allergy Clin Immunol* 2013;131(3):646-57.
46. Chapman DG, Irvin CG, Kaminsky DA, Forgione PM, Bates JH, Dixon AE. Influence of distinct asthma phenotypes on lung function following weight loss in the obese. *Respirology* 2014;19(8):1170-7.
47. Goldman MD, Saadeh C, Ross D. Clinical applications of forced oscillation to assess peripheral airway function. *Respir Physiol Neurobiol* 2005;148(1-2):179-94.
48. Boulet LP. Influence of obesity on the prevalence and clinical features of asthma. *Clin Invest Med* 2008;31(6):E386-90.
49. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *Bmj* 2000;320(7238):827-32.
50. Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. *Chest* 2000;118(5):1315-21.
51. Aaron SD, Fergusson D, Dent R, Chen Y, Vandemheen KL, Dales RE. Effect of weight reduction on respiratory function and airway reactivity in obese women. *Chest* 2004;125(6):2046-52.
52. Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, Wood LG. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. *Clin Exp Allergy* 2013;43(1):36-49.
53. Heacock T, Lugogo N. Role of Weight Management in Asthma Symptoms and Control. *Immunol Allergy Clin North Am* 2014;34(4):797-808.
54. Reddy RC, Baptist AP, Fan Z, Carlin AM, Birkmeyer NJ. The effects of bariatric surgery on asthma severity. *Obes Surg* 2011;21(2):200-6.
55. Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin MJ, Schwab M, Pollak M, Zhang Y, Yu Y, Becker KG, Bohr VA, Ingram

DK, Sinclair DA, Wolf NS, Spindler SR, Bernier M, de Cabo R. Metformin improves healthspan and lifespan in mice. *Nat Commun* 2013;4:2192.

56. Calixto M, Lintomen L, Schenka A, Saad MJ, Zanesco A, Antunes E. Obesity enhances eosinophilic inflammation in a murine model of allergic asthma. *Br J Pharmacol* 2013;159(3):617-25.
57. Shore SA, Williams ES, Zhu M. No effect of metformin on the innate airway hyperresponsiveness and increased responses to ozone observed in obese mice. *J Appl Physiol* 2008;105(4):1127-33.
58. Huang CC, Chan WL, Chen YC, Chen TJ, Chou KT, Lin SJ, Chen JW, Leu HB. Statin use in patients with asthma: a nationwide population-based study. *Eur J Clin Invest* 2011;41(5):507-12.
59. Zeki AA, Oldham J, Wilson M, Fortenko O, Goyal V, Last M, Last A, Patel A, Last JA, Kenyon NJ. Statin use and asthma control in patients with severe asthma. *BMJ Open* 2013;3(8).

ADDENDUM

NEDERLANDSE SAMENVATTING
ABBREVIATIONS
PUBLICATIONS
CURRICULUM VITAE

NEDERLANDSE SAMENVATTING

Historisch werd zwaarlijvigheid, ook wel obesitas genoemd, gezien als een teken van rijkdom en welvaart. Het is aannemelijk om te veronderstellen dat obesitas tegelijkertijd ontstond met de industriële revolutie. Dat obesitas ook kan leiden tot een scala aan andere aandoeningen, werd al veel eerder onderkend: het was Hipprocrates die al schreef dat "zwaarlijvigheid niet alleen zelf een ziekte is, maar de voorbode van andere"[1]. Obesitas is momenteel een groot gezondheidsprobleem en ontwikkelt zich tot een wereldwijde epidemie. Obesitas wordt geclassificeerd middels de Body Mass Index (BMI), en is gedefinieerd als een abnormale of excessieve vetophoping die gezondheidsproblemen kan veroorzaken. De Wereld Gezondheid Organisatie voorspelt dat in 2015 ongeveer 2,3 miljard volwassenen overgewicht (BMI 25-30 kg/m^2) zullen hebben, en dat meer dan 700 miljoen obees zullen zijn (BMI 30-40 kg/m^2). Een BMI boven de 40 kg/m^2 wordt ook wel morbide obesitas genoemd.

De afgelopen decades is het aantal patiënten met astma ook toegenomen[2, 3]. Omdat de "epidemie" van obesitas gelijktijdig heeft plaats gevonden, suggereert dit een mogelijke relatie tussen obesitas en astma[4, 5]. Daarnaast hebben obese astma-patiënten een slechtere astma gerelateerde kwaliteit van leven[6], meer klachten ten gevolge van minder astma controle[7] en ook ernstiger ziekte[8]. Het feit dat astma symptomen verminderen na gewichtsverlies, ondersteunt de gedachte dat obesitas ook daadwerkelijk leidt tot astma, oftewel dat er een causale relatie bestaat[5]. Het dilemma waar dit proefschrift antwoord op probeert te geven, is of de relatie tussen obesitas en astma causaal is, of dat obesitas en astma twee tegelijk voorkomende ziekten in dezelfde persoon zijn.

Diagnose van astma in morbide obese patiënten

Volgens de laatste Global Initiative for Asthma (GINA) definitie van 2014, is astma een ziekte die zich op meerdere manieren kan uiten ("heterogene ziekte"), en wordt meestal gekarakteriseerd door chronische luchtwegontsteking. Het wordt gedefinieerd door klachten zoals piepen, kortademigheid, benauwdheid en hoesten. Deze klachten zijn niet altijd aanwezig, maar komen en gaan zowel over de tijd als in intensiteit. Als ten tijde van klachten een longfunctie zou worden geblazen, zou dit een moeizame uitademing laten zien omdat de luchtwegen vernauwd zijn, terwijl er geen afwijkingen zullen zijn als men geen klachten heeft. Dit wordt ook wel een "variabele expiratoire luchtweg obstructie" genoemd[9]. De GINA richtlijn adviseert dat de diagnose van astma zowel gebaseerd moet zijn op de aanwezigheid van symptomen als objectieve metingen zoals variabele expiratoire luchtweg obstructie[9]. Echter, in de dagelijkse praktijk en met name in de 1^e lijn, is de diagnose astma voornamelijk gebaseerd op klachten; longfunctieonderzoek (spirometrie of provocatietesten) worden niet altijd uitgevoerd[10]. Omdat obese mensen meer klachten van kortademigheid hebben dan niet-obese mensen[11],

kan het gebeuren dat zij ten onrechte de diagnose astma krijgen (overdiagnose). Onvermijdelijk leidt elke overdiagnose tot ineffectieve behandeling[10], met verhoogde kans op bijwerkingen en hoge medische kosten[12].

De eerste suggestie dat er een relatie bestond tussen obesitas en astma was gebaseerd op epidemiologische studies, waarbij er in grote groepen mensen gekeken werd hoe vaak een ziekte voorkwam. Echter, vele epidemiologische studies naar obesitas en astma hebben een huisarts-diagnose astma gebruikt, zonder bevestiging van de diagnose astma middels longfunctietesten. Dit betekent dat men kritisch moet zijn of de diagnose astma wel correct is, en het roept ook vraagtekens op bij de mogelijke *causale* relatie tussen obesitas en astma. Andere studies hebben namelijk al laten zien dat na uitgebreide testen de diagnose astma verkeerd was bij 30% van de door de huisarts gediagnosticeerde astma patiënten[13]. Aan de andere kant is het missen van de diagnose astma (onderdiagnose) in de obese populatie ook een belangrijk aspect. Alle voorgaande studies betreffende overdiagnose selecteerden obese patiënten met waarbij de diagnose astma is vastgesteld[13-15], en namen daardoor de obese patiënten met ongediagnosticeerd astma niet mee in hun analyses. Daarom is er weinig bekend over onderdiagnose van astma bij obese personen. In **hoofdstuk 2** hebben we laten zien dat zowel overdiagnose maar ook onderdiagnose van astma voorkomt in morbide obese patiënten. Dit bevestigt nogmaals dat bij morbide obese patiënten het stellen van de diagnose astma op basis van alleen symptomen onbetrouwbaar is, en dat longfunctietesten een essentieel onderdeel zijn van de diagnostiek naar astma in de morbide obese populatie[16]. Echter, als gevolg van het selectieproces en de inclusiemethoden van onze studie van hoofdstuk 2, kunnen we geen uitspraak doen over de frequentie van overdiagnose danwel onderdiagnose van astma in de totale morbide obese populatie.

Bronchiale en systemische inflammatie bij morbide obese patiënten

Omdat overdiagnose van astma niet geheel de associatie tussen obesitas en astma kan verklaren, zijn we op zoek gegaan naar andere verklaringen. In **hoofdstuk 3** werden alle tot dan toe bekende verklaringen besproken, zoals dieet, genetica, andere ziekten die tegelijkertijd spelen in een patiënt (comorbiditeiten), veranderde longfunctie ten gevolge van de andere lichaamsbouw (centrale adipositas) en ontsteking. Zoals al eerder gezegd is chronische luchtwegontsteking een essentieel onderdeel van astma. Luchtwegontsteking wordt ook wel bronchiale inflammatie genoemd. Er zijn verschillende vormen van ontsteking, oftewel inflammatie, zoals onder andere "systemische inflammatie". Hiermee wordt een ontsteking bedoeld die zich afspeelt in het gehele lichaam ("het systeem"), en die zich verspreid door het lichaam via het bloed.

In hoofdstuk 3 werd als een mogelijke nieuwe verklaring voor de relatie tussen obesitas en astma het metabool syndroom gesuggereerd[17]. Het metabool syndroom is een combinatie van ziekten die vaak voorkomt bij mensen met overgewicht. We spreken

van het metabool syndroom als patiënten 3 van de volgende 5 problemen hebben; suikerziekte (diabetes mellitus), hoge bloeddruk (hypertensie), hoog cholesterol (hypertrygliceridemie), te laag "goed cholesterol" (verlaagd HDL cholesterol) of een te grote buikomtrek (centrale adipositas).

De mechanismen die ten grondslag liggen aan de relatie tussen het metabool syndroom en astma zijn nog onduidelijk. We weten dat personen met obesitas een milde chronische systemische inflammatie hebben, wellicht dat deze milde chronische systemische inflammatie de relatie tussen obesitas en astma verklaard. De hypothese is dat deze milde systemische inflammatie, via het bloed "overstroomt" naar de longen, en aldaar de voor astma zo typische chronische luchtweginflammatie veroorzaakt.

Om te onderzoeken of het metabool syndroom inderdaad de relatie tussen obesitas en astma verklaart, hebben we in **hoofdstuk 4** de relatie tussen luchtwegobstructie (FEV_1/FVC) – een essentieel onderdeel van de diagnose van astma – en het metabool syndroom onderzocht. We hebben onder andere gekeken naar eosinofielen; dit zijn een specifiek soort ontstekingscellen, die vaak verhoogd zijn bij patiënten met allergieën en astma. Deze studie liet een klein, maar statistisch significant, verschil zien in eosinofielen en luchtwegobstructie (FEV_1/FVC) tussen patiënten met en zonder het metabool syndroom[18]. Ondanks dat het verschil maar gering is, kan het wel onze hypothese - dat het metabool syndroom mogelijk longfunctiestoornissen veroorzaakt, door de systemische inflammatie, en met name, door bloed eosinofielen - ondersteunen. Dit zou een aanwijzing kunnen zijn voor een causale relatie tussen obesitas en astma, en dan wellicht via het metabool syndroom.

Nadat we indirect bewijs hadden gevonden dat systemische inflammatie mogelijk de relatie tussen astma en obesitas zou kunnen verklaren, hebben we onderzocht of deze systemische inflammatie ook daadwerkelijk leidt tot lokale bronchiale inflammatie. Zoals al eerder vermeld, is astma een chronische ontsteking van de luchtwegen. Typisch allergisch astma wordt gekarakteriseerd door de aanwezigheid van een allergie, een verhoogd aantal eosinofielen in het slijm van de luchtwegen en verhoogd uitgeademd stikstofoxide ("T_H2-mechanisme"). Astma is echter een heterogene ziekte, wat betekent dat er verschillende vormen van astma zijn. Voor elk van deze verschillende vormen van astma, ook wel astma fenotypes genoemd, zijn er verschillende onderliggende ziekteprocessen die mogelijk deels op een andere manier behandeld zouden moeten worden[9]. Astma met obesitas is een van deze herkenbare fenotypes, meestal gekarakteriseerd door veel symptomen, die pas tot uiting komen op volwassen leeftijd. Er is in de literatuur enige discussie over welke ontstekingscellen betrokken zijn bij de luchtwegontsteking bij obese astma patiënten. In tegenstelling tot de typisch allergische astma patiënten, is er vaak géén sprake van een verhoogd aantal eosinofielen, maar wordt er gedacht dat de neutrofielen de inflammatie veroorzaken. Terwijl de ene onder-

zoeksgroep meer neutrofielen in het slijm van de luchwegen laat zien[19], laten andere studies geen relatie zien tussen obesitas en neutrofiele luchtweginflammatie[20, 21]. Er zijn echter verschillende manieren om de cellen betrokken bij de luchtwegontsteking te onderzoeken. Andere studies hebben luchtwegontsteking onderzocht door het spoelen van de longen met vocht ("bronchiale lavage") of het maken van een uitstrijkje van de luchtwegen ("bronchiale brushes"). Daarom kan de vraag worden gesteld of zij werkelijk luchtwegontsteking hebben onderzocht. Er kan namelijk een verschil zijn in de ontstekingscellen aangetroffen in het slijmvlies van de luchtwegen ("luchtweg epitheel"; zoals onderzocht met lavage, brushes of bronchiale biopten) en de cellen van de wanden van de luchtwegen zelf ("submucosa"). Door middel van het bestuderen van stukjes weefsel die worden weggenomen uit de wand van de luchtwegen ("bronchiale biopten"), kunnen de ontstekingscellen in de wanden van de luchtwegen worden onderzocht.

We hebben in **hoofdstuk 5** de karakteristieken van bronchiale biopten van morbide obese astma patiënten en morbide obese controles onderzocht. Tot onze verrassing vonden we geen bewijs voor méér luchtwegontsteking (verhoogde aantallen eosinofielen of neutrofielen) in morbide obese astma patiënten in vergelijking met morbide obese patiënten zonder astma. Dit ondanks dat we wel bewijs hadden voor meer systemische inflammatie in morbide obese astma patiënten, waarbij patiënten met meer astmaklachten ook meer systemische inflammatie hadden[22]. Onze data suggereren dat astma in ons cohort niet wordt aangestuurd door het klassieke T_H2-gemedieerde mechanisme waarbij eosinofielen een belangrijke rol spelen, en wellicht gezien moet worden als een specifiek fenotype van de ziekte zonder significant waarneembare ontsteking in de luchtwegen. Wellicht is het zelfs zo dat astma in *morbide obese* patiënten een specifiek fenotype is, dat onderscheiden moet worden van astma in *obese* patiënten.

Bariatrische chirurgie

Onder bariatrische chirurgie worden alle operaties verstaan die tot doel hebben om het gewicht te verminderen. Bariatrische chirurgie wordt gezien als een definitieve oplossing voor morbide obesitas, omdat het gewichtsverlies permanent is. Dit in tegenstelling tot diëten, die vaak een tijdelijke oplossing bieden. Bariatrische chirurgie leidt tot gewichtsverlies middels twee mechanismen: minder opname van voedingsstoffen (malabsorptie) en een kleinere hoeveelheid voedsel die kan worden gegeten (restrictie). De sleeve gastrectomy, waarbij het grootste deel van de maag wordt verwijderd, is een restrictieve methode. Bij de gastric bypass operatie wordt een klein zakje gemaakt van de maag, gescheiden van de rest van de maag, en tevens aangesloten op de dunne darm. Dit is een combinatie van zowel een restrictieve als malabsorptieve procedure.

Tegelijkertijd met de obesitas epidemie, is ook het aantal bariatrische chirurgie procedures toegenomen, met een 22-voudige stijging tussen 1996 en 2008[23]. Bij ongeveer 5% zullen er complicaties optreden. In een grote studie werd aangetoond dat longont-

steking en longfalen, ondanks dat deze niet vaak voorkomen, wel voor één-vijfde van de morbiditeit zorgen. Daarnaast zijn juist deze complicaties geassocieerd met de hoogste kans op overlijden[24] en de hoogste kosten[25]. Omdat bariatrische chirurgie niet wordt verricht vanwege een acuut levensgevaar, maar een electieve procedure is in relatief gezonde patiënten, is preventie van complicaties van bariatische chirurgie van groot belang.

Huidige richtlijnen stellen dat longfunctietesten voor de operatie niet standaard nodig zijn bij patiënten zonder bewijs voor longziekten[26]. In hoofdstuk 2 hebben we reeds laten zien dat symptomen passend bij luchtwegziekten vaak onbetrouwbaar zijn in morbide obese patiënten, maar ook dat kortademigheid soms ten onrechte wordt toegewijd aan obesitas in plaats van astma (onderdiagnose). Dit alles tezamen was de reden om in een cohort te kijken naar de relatie tussen longfunctiestoornissen en complicaties van bariatrische chirurgie. In **hoofdstuk 6** hebben we laten zien dat patiënten met complicaties binnen 30 dagen na bariatrische chirurgie vaker luchtweg-reversibiliteit of luchtwegobstructie hebben[27]. Wij zijn dan ook van mening dat, juist omdat symptomen passend bij luchtwegziekten vaak onbetrouwbaar zijn in de morbide obese populatie, longfunctietesten een routinematig onderdeel zouden moeten zijn van de pre-operatieve risico inschatting.

Zover wij weten zijn er zes prospectieve studies gepubliceerd die hebben gekeken naar het effect van bariatrische chirurgie bij obese astma patiënten[28-33]. Deze zes studies concluderen dat luchtwegfunctie en astma controle sterk verbeteren met gewichtsverlies na bariatrische chirurige bij obese astma patiënten. Echter, de aantallen onderzochte patiënten in deze zes studies waren maar klein. Daarnaast hadden ze of geen (follow-up) van een controle groep van niet-astma patiënten na bariatrische chirurgie of geen controle groep van obese astma patiënten die geen bariatrische chirurgie ondergingen.

In **hoofdstuk 7** hebben we uitgebreid gekeken naar zowel klachten als allerlei klinische parameters, systemische en bronchiale ontsteking voor en na bariatrische chirurgie in morbide obese astma patiënten en morbide obese controles[34]. Ondanks dat we geen verbetering vonden in luchtwegobstructie (onze primaire uitkomstparameter FEV_1/FVC), vonden we wel verbetering in astma-controle (gemeten met de ACQ vragenlijst), kwaliteit van leven, medicatie-gebruik en bronchiale hyperreactiviteit (longen die te sterk reageren op prikkelende stoffen, uitgedrukt middels PD_{20} metacholine). De significante verbetering in kleine luchtwegen functie (R_5-R_{20}) na bariatrische chirurgie, welke geassocieerd was met BMI, ACQ en PD_{20}, suggereert dat de kleine luchtwegen een grote rol spelen in de relatie tussen obesitas en astma. Tenslotte daalden na bariatrische chirurgie ook de markers van systemische ontsteking, en het aantal mestcellen (een type ontstekingscellen) in de luchtwegen van obese astma-patiënten. Tezamen bena-

drukken deze resultaten dat door bariatrische chirurgie geïnduceerd gewichtsverlies de hoeksteen van de behandeling van morbide obese astma patiënten zou moeten zijn.

De studies uit dit proefschrift laten zien dat de interacties tussen obesitas en astma een complex karakter hebben. De epidemiologische relatie tussen astma en obesitas bewijst geen causaliteit, en kan niet geheel verklaard worden door overdiagnose van astma, zeker omdat ook onderdiagnose van astma voorkomt binnen de obese populatie. Het benadrukt nogmaals de noodzaak tot een strikte diagnose van astma bij morbide obese personen. Het feit dat we een relatie vonden tussen luchtwegobstructie en eosinofielen in het perifere bloed, met name bij patiënten met het metabool syndroom, wijst weer op een mogelijke causale relatie tussen obesitas en astma. Dit werd echter weer tegengesproken door het feit dat we geen verschil in bronchiale inflammatie vonden tussen morbide obese patiënten met of zonder astma. Ondanks dat we wel aanwijzingen vonden voor meer systemische inflammatie, vonden we dus geen pathofysiologische verklaring in de bronchus biopten waarom deze patiënten "astma" hebben. Daarmee rijst de vraag of astma bij *morbide* obese populatie een specifiek fenotype is, zonder eosinofiel of neutrofiel gedreven inflammatie. Echter, ondanks de afwezigheid van bronchiale inflammatie, lijkt substantieel gewichtsverlies door bariatrische chirurgie longfunctie, kwaliteit van leven en systemische inflammatie te verbeteren bij zowel morbide obese astma patiënten als morbide obese controles. Dit houdt in dat gewichtsverlies de hoeksteen van de behandeling van het morbide obese astma fenotype is. En deze temporale relatie is weer een aanwijzing voor een causale relatie tussen obesitas en astma.

Een goede verklaring waarom de ene morbide obese patiënt wel "astma" heeft en de ander niet, hebben we nog niet gevonden. Ondanks onze eerdere aanwijzingen voor een mogelijke rol voor het metabool syndroom, konden we deze niet terugvinden in beide studies met bronchusbiopten. Daarnaast kan het zijn dat obesitas een factor is die astma verergert, maar niet veroorzaakt. Wellicht dat de kleine luchtwegen hier toch een grotere rol in spelen. Middels longfunctieonderzoek hebben we hier wel aanwijzingen voor gevonden. Met name centrale adipositas – oftewel de appelvorm in tegenstelling tot de peervorm – zou compressie kunnen geven op de kleine luchtwegen.

Omdat gewichtsreductie een belangrijk onderdeel van de behandeling is, zou mijns inziens astma, net als hypertensie of diabetes mellitus, een van de ziekten moeten worden waarbij bariatrische chirurgie al geïndiceerd is vanaf een BMI van 35 kg/m^2. Nader onderzoek is nodig om aan te tonen of de bovengenoemde effecten van bariatrische chirurgie ook blijven bestaan na langere follow-up. Ook onderzoek naar de rol van de kleine luchtwegen bij morbide obese astma patiënten is noodzakelijk. Tenslotte, is het effect van longrevalidatie voor bariatrische chirurgie een interessant onderwerp van verder onderzoek, en kan het mogelijk tonen of longrevalidatie het aantal complicaties

na bariatrische chirurgie kan verlagen, en aantonen of longrevalidatie überhaupt enig effect heeft bij (morbide) obese astma patiënten.

Alles tezamen genomen, ben ik ondanks het feit dat nader onderzoek naar met name de rol van de kleine luchtwegen nodig is, van mening dat er een causale relatie bestaat tussen obesitas en astma.

REFERENTIES

1. Haslam DW, James WP. Obesity. *Lancet* 2005;366(9492):1197-209.
2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31(1):143-78.
3. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355(21):2226-35.
4. Chinn S. Asthma and obesity: where are we now? *Thorax* 2003;58(12):1008-10.
5. Camargo CA, Jr., Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;159(21):2582-8.
6. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med* 2006;100(4):648-57.
7. Saint-Pierre P, Bourdin A, Chanez P, Daures JP, Godard P. Are overweight asthmatics more difficult to control? *Allergy* 2006;61(1):79-84.
8. Taylor B, Mannino D, Brown C, Crocker D, Twum-Baah N, Holguin F. Body mass index and asthma severity in the National Asthma Survey. *Thorax* 2008;63(1):14-20.
9. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014. *Available from: http://www.ginasthma.org/.* 2014.
10. Lucas AE, Smeenk FW, Smeele IJ, van Schayck CP. Overtreatment with inhaled corticosteroids and diagnostic problems in primary care patients, an exploratory study. *Fam Pract* 2008;25(2):86-91.
11. Pakhale S, Doucette S, Vandemheen K, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Aaron SD. A comparison of obese and nonobese asthmatics: Exploring an asthma-obesity interaction. *Chest* 2010;137(6):1316-1323.
12. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, FitzGerald JM. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
13. Scott S, Currie J, Albert P, Calverley P, Wilding JP. Risk of mis-diagnosis, Health related Quality of Life and Body Mass Index in Overweight Patients with doctor diagnosed asthma. *Chest* 2012; 141(3):616-24.
14. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Doucette S, Fergusson D. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179(11):1121-31.
15. Luks VP, Vandemheen KL, Aaron SD. Confirmation of asthma in an era of overdiagnosis. *Eur Respir J* 2010;36(2):255-60.
16. van Huisstede A, Castro Cabezas M, van de Geijn GJ, Mannaerts GH, Njo TL, Taube C, Hiemstra PS, Braunstahl GJ. Underdiagnosis and overdiagnosis of asthma in the morbidly obese. *Respir Med* 2013;107(9):1356-64.
17. van Huisstede A, Braunstahl GJ. Obesity and asthma: co-morbidity or causal relationship? *Monaldi Arch Chest Dis* 2011;73(3):116-23.
18. van Huisstede A, Cabezas MC, Birnie E, van de Geijn GJ, Rudolphus A, Mannaerts G, Njo TL, Hiemstra PS, Braunstahl GJ. Systemic inflammation and lung function impairment in morbidly obese subjects with the metabolic syndrome. *J Obes* 2013;2013:131349.
19. Scott HA, Gibson PG, Garg ML, Wood LG. Airway Inflammation is Augmented by Obesity and Fatty Acids in Asthma. *Eur Respir J* 2011;38(3):594-602.
20. Todd DC, Armstrong S, D'Silva L, Allen CJ, Hargreave FE, Parameswaran K. Effect of obesity on airway inflammation: a cross-sectional analysis of body mass index and sputum cell counts. *Clin Exp Allergy* 2007;37(7):1049-54.

21. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? *Chest* 2008; 134(2):317-23.
22. van Huisstede A, Rudolphus A, van Schadewijk A, Cabezas MC, Mannaerts GH, Taube C, Hiemstra PS, Braunstahl GJ. Bronchial and systemic inflammation in morbidly obese subjects with asthma: a biopsy study. *Am J Respir Crit Care Med* 2014;190(8):951-4.
23. Buchwald H, Oien DM. Metabolic/bariatric surgery Worldwide 2008. *Obes Surg* 2009;19(12):1605-11.
24. Gupta PK, Gupta H, Kaushik M, Fang X, Miller WJ, Morrow LE, Armour-Forse R. Predictors of pulmonary complications after bariatric surgery. *Surg Obes Relat Dis* 2011;8(5):574-81.
25. Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA, Jr. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. *J Am Coll Surg* 2004;199(4):531-7.
26. Chetta A, Tzani P, Marangio E, Carbognani P, Bobbio A, Olivieri D. Respiratory effects of surgery and pulmonary function testing in the preoperative evaluation. *Acta Biomed* 2006;77(2):69-74.
27. van Huisstede A, Biter LU, Luitwieler R, Castro Cabezas M, Mannaerts G, Birnie E, Taube C, Hiemstra PS, Braunstahl GJ. Pulmonary function testing and complications of laparoscopic bariatric surgery. *Obes Surg* 2013;23(10):1596-603.
28. Maniscalco M, Zedda A, Faraone S, Cerbone MR, Cristiano S, Giardiello C, Sofia M. Weight loss and asthma control in severely obese asthmatic females. *Respir Med* 2008;102(1):102-8.
29. Dixon AE, Pratley RE, Forgione PM, Kaminsky DA, Whittaker-Leclair LA, Griffes LA, Garudathri J, Raymond D, Poynter ME, Bunn JY, Irvin CG. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011;128(3):508-15 e1-2.
30. Lombardi C, Gargioni S, Gardinazzi A, Canonica GW, Passalacqua G. Impact of bariatric surgery on pulmonary function and nitric oxide in asthmatic and non-asthmatic obese patients. *J Asthma* 2011;48(6):553-7.
31. Boulet LP, Turcotte H, Martin J, Poirier P. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respir Med* 2012;106(5):651-60.
32. Al-Alwan A, Bates JH, Chapman DG, Kaminsky DA, DeSarno MJ, Irvin CG, Dixon AE. The nonallergic asthma of obesity. A matter of distal lung compliance. *Am J Respir Crit Care Med* 2014;189(12): 1494-502.
33. Sideleva O, Suratt BT, Black KE, Tharp WG, Pratley RE, Forgione P, Dienz O, Irvin CG, Dixon AE. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. *Am J Respir Crit Care Med* 2012;186(7):598-605.
34. van Huisstede A, Rudolphus A, Castro Cabezas M, Biter LU, van de Geijn GJ, Taube C, Hiemstra PS, Braunstahl GJ. Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma. *Thorax* 2015;70(7):659-67

ABBREVIATIONS

%EWL: percentage excess weight loss
ACQ: Asthma Control Questionnaire
AQLQ: Asthma Quality of Life Questionnaire
ASA: American Society of Anesthesiologists
BHR: bronchial hyperresponsiveness
BMI: Body Mass Index
COPD: chronic obstructive pulmonary disease
CRP: C-reactive protein
DLCO: diffusion capacity
eNO: exhaled Nitric Oxide
ERV: expiratory reserve volume
ESS: Epworth Sleepiness Scale
FEF_{25-75} : Forced expiratory flow at 25% point to the 75% point of Forced Vital Capacity
Fe_{NO}: fraction of Exhaled Nitric Oxide
FEV_1: Forced Expiratory Volume in 1 second
FRC: Functional Respiratory Capacity
FVC: Forced Vital Capacity
GERD: Gastroesophageal reflux disease
HDL: High-density lipoprotein
hs-CRP: high sensitivity C-reactive protein
ICS: inhaled corticosteroid
IL: interleukin
IOS: impulse oscillometry
NCEP-APT III: National Cholesterol Education Program's Adult Treatment Panel III report
OSAS: Obstructive Sleep Apnea Syndrome
RV: Residual volume
SPT: skin prick test
TLC: Total Lung Capacity
WHO: World Health Organisation

PUBLICATIONS

Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma.
van Huisstede A, Rudolphus A, Castro Cabezas M, Biter LU, van de Geijn GJ, Taube C, Hiemstra PS, Braunstahl GJ.
Thorax, 2015;70(7):659-667

Bronchial and systemic inflammation in morbidly obese asthmatic subjects: a biopsy study.
Van Huisstede A, Rudolphus A, van Schadewijk A, Castro Cabezas M, Mannaerts GHH, Taube C, Hiemstra PS, Braunstahl GJ.
Am J Respir Crit Care Med, 2014;190(8):951-4.

Underdiagnosis and overdiagnosis of asthma in the morbidly obese
Van Huisstede A, Castro Cabezas M, van de Geijn GJ, Mannaerts GH, Njo TL, Taube C, Hiemstra PS, Braunstahl GJ.
Respiratory Medicine, 2013;107(9):1356-64.

Pulmonary function testing and complications of laparoscopic bariatric surgery.
Van Huisstede A, Biter LU, Luitwieler R, Castro Cabezas M, Mannaerts G, Birnie E, Taube C, Hiemstra PS, Braunstahl GJ.
Obesity Surgery, 2013;23(10):1596-603.

Systemic inflammation and lung function impairment in morbidly obese subjects with the metabolic syndrome
Van Huisstede A, Cabezas MC, Birnie E, van de Geijn GJ, Rudolphus A, Mannaerts G, Njo TL, Hiemstra PS, Braunstahl GJ.
Journal of Obesity, 2013;2013:131349.

Morbidly obese human subjects have increased peripheral blood CD4+ T cells with skewing toward a Treg- and Th2-dominated phenotype.
Van der Weerd K, Dik WA, Schrijver B, Schweitzer DH, Langerak AW, Drexhage HA, Kiewiet RM, Van Aken MO, **van Huisstede A**, van Dongen JJ, van der Lelij AJ, Staal FJ, Van Hagen PM.
Diabetes, 2012;61(2):401-8.

Obesity and asthma: co-morbidity or causal relationship?
Van Huisstede A, Braunstahl GJ.

Monaldi Archives Chest Disease, 2010;73-(3):116-23. Review.

Systemische inflammatie bij obesitas en astma
Van Huisstede A, Braunstahl GJ
Ned Tijdschr Allergie & Astma 2010;4:156-164

Geeft obesitas een grotere kans op astma, en wat is het mechanisme?
Van Huisstede A, Braunstahl GJ
Spreekuur Longziekten; jaargang 1, nr 8, 2010

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Astrid Aardenburg – van Huisstede was born on May 1th 1982 in Leidschendam, the Netherlands. In 2000 she graduated from the Alfrink College, Zoetermeer, the Netherlands, and she received her first-year diploma Medical Imaging and Radiotherapeutic Techniques at the College of Haarlem in 2001. Subsequently, she began medical school at the Erasmus University in Rotterdam. After receiving her medical degree in October 2007, she started as a resident Internal Medicine at the Sint Franciscus Gasthuis in Rotterdam until September 2009.

The beginning of her PhD project at the Departments of Pulmonology of the Sint Franciscus Gasthuis and Leiden University Medical Center with Prof. dr. P.S. Hiemstra, Prof. dr. C. Taube and Dr. G.J. Braunstahl, was in September 2009 of which the results are described in this thesis. From January 2013, she has started her residency training in Internal Medicine at the Sint Franciscus Gasthuis, Rotterdam under supervision of dr. A.P. Rietveld. Followed by her specialty training in Pulmonology from January 2015 in the Sint Franciscus Gasthuis, supervised by dr. J.C.C.M. In 't Veen and dr. G.J. Braunstahl.