Difficult-to-treat asthma : mechanisms and risk factors

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Chapter 5

Airway inflammation in obese and non-obese patients with difficult-to-treat asthma

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Abstract

Background: Asthma and obesity are associated disorders, but the contribution of obesity to difficult-to-treat asthma as well as the mechanisms responsible for this relationship are unclear. The aim of this study was to investigate the relationship between obesity (body mass index (BMI) ≥ 30) and factors related with asthma severity in patients with difficult-to-treat asthma.

Methods: 136 non-smoking asthmatic adults with persistent symptoms despite high doses of inhaled or oral corticosteroids and long-acting bronchodilators were studied (70% female, median (range) age 44.6 (18-75), 32% on daily oral corticosteroids). The association between obesity, lung function parameters (FEV_1, FRC/TLC), inflammatory markers (blood eosinophils, sputum eosinophils and neutrophils, exhaled nitric oxide (FeNO), airway hyperresponsiveness, C-reactive protein (CRP) and aggravating co-morbid factors (severe chronic sinus disease, gastroesophageal reflux, recurrent respiratory infections, psychopathology and obstructive sleep apnoea) was investigated.

Results: Obese patients (n=29) had a higher FEV_1%pred (p=0.05) and a lower FRC/TLC% pred (p<0.01) compared to non-obese patients (n=107). BMI was inversely related to sputum eosinophils (r= -0.36, p<0.01) and FeNO (r= -0.30, p<0.01). Obese patients had an increased risk for gastroesophageal reflux (OR:2.3) and sleep apnoea (OR:3.1).

Conclusions: Obesity in patients with difficult-to-treat asthma is inversely related to sputum eosinophils and FeNO, and positively associated with the presence of co-morbid factors and reduced lung volumes. This suggests that other factors than airway inflammation alone explain the relationship between obesity and asthma severity.

Introduction

There is increasing evidence that asthma and obesity are associated disorders (1). Obesity has been demonstrated to be a risk factor for incident asthma and is associated with an increased prevalence of asthma symptoms (2;3). Obesity also appears to play a role in asthma severity and control. Studies have shown that severe asthma is more prevalent in overweight patients as compared to normal weight patients (4) and that body mass index (BMI) is positively associated with clinical asthma severity (5). In addition, patients with more severe asthma have higher BMI than those with milder asthma (4;6). Thus, obesity seems to be related with asthma severity but the mechanisms responsible for this relationship are not yet clarified.

Several mechanisms may play a role in modulating the relationship between obesity and asthma severity and control. Obesity has mechanical effects on lung function, it leads to a systemic proinflammatory state, thereby potentially increasing airway inflammation, and is associated with a number of co-morbid factors which might interfere with asthma control (7;8).

In the present study, we hypothesized that obesity contributes to difficult-to-treat asthma by altering lung volumes, enhancing airway inflammation and aggravating co-morbid conditions. The aim of this study was therefore to examine the association between obesity and lung function parameters (forced expiratory volume in one second (FEV_1), functional residual capacity/total lung capacity (FRC/TLC)), markers of systemic and airway inflammation (blood eosinophils, sputum eosinophils and neutrophils, exhaled nitric oxide (FeNO), airway hyperresponsiveness, C-reactive protein (CRP)) and co-morbid conditions (chronic sinus disease, gastroesophageal reflux, respiratory infections, psychopathology and obstructive sleep apnoea).

Methods

Subjects

One hundred and thirty-six patients, aged 18-75 years, with difficult-to-treat asthma according to the definition of the European Respiratory Society Task Force (9), were consecutively recruited from the outpatient pulmonary departments of 10 hospitals in the western region of The Netherlands. The participating patients had a history of episodic dyspnoea and wheezing, a documented (recently or in the past) reversibility in FEV_1 >12% predicted and/or hyperresponsiveness to inhaled histamine. Patients were all treated with

≥ 1600 µg/day beclomethasone or equivalent and long-acting bronchodilators for >1 year, and were all nonsmokers (smoking history ≤ 10 pack-years). They were all symptomatic and had experienced at least one severe exacerbation during the past year requiring a course of oral corticosteroids or were on maintenance therapy with oral prednisone. The study was approved by the Hospital Medical Ethics Committee, and all patients gave written informed consent. Previous investigations in this patient cohort have been published elsewhere (10-12).

Measurements

Lung function parameters

Forced expiratory volume in one second (FEV_1) was assessed before and 30 minutes after the inhaled administration of 400 µg salbutamol and 80 µg ipratropium bromide. Functional residual capacity (FRC) and total lung capacity (TLC) were measured by the multiple-breath helium equilibration method. All lung function parameters were expressed as percentage of predicted value (13).

Markers of systemic and airway inflammation

Eosinophils in blood were measured by standard automated cell counter. Sputum was induced and processed according to a validated protocol (14), using the "full sample"-method. Saline solutions were inhaled 3 times for 5 minutes with frequent monitoring of the FEV_1. Differential cell counts were performed on cytospins.

Exhaled nitric oxide (FeNO) measurements were performed by standardized method (15), using a chemiluminescence analyzer (Sievers NOA 270B; Boulder, CO, USA). After inhaling "NO-free" air (< 2ppb) from residual volume to total lung capacity, subjects performed a slow expiratory vital capacity manoeuvre with a constant expiratory flow rate of 100 ml/sec (standard at the time of study initiation). Plateau levels of FeNO against time were determined and expressed as parts per billion (ppb). Airway hyperresponsiveness to histamine, expressed as provocative concentration to cause a 20% fall in FEV_1 (PC_{20} histamine) was measured using a tidal breathing standardized procedure (16). High sensitivity C-reactive protein (hs-CRP) in blood was measured by Elisa, with a lower detection limit of 0.5mg/L.

Aggravating co-morbid factors

Paranasal sinus disease was considered a potential aggravating factor, if there was an indication for functional endoscopic sinus surgery, as judged by an independent ENT specialist. For this purpose, nasal endoscopy and standardized CT-scanning was performed. Gastroesophageal reflux was demonstrated by a 24-h pH measurement of the oesophagus (17) or dependency on proton-pump inhibitors. Recurrent respiratory infections were

defined as ≥ 3 episodes in the past two years of increased dyspnoea, cough and purulent sputum for which antibiotic courses were prescribed. Psychologic dysfunctioning was defined as a score ≥ 6 on the short General Health Questionnaire (GHQ-12) (18). Obstructive sleep apnoea was assessed by polysomnography, or by heavy snoring and frequent apnoea periods of >10 sec (19) reported by the partner in combination with a history of daytime sleepiness.

Analysis

Blood eosinophils, sputum eosinophils and neutrophils, FeNO and PC_{20} histamine were log-transformed before analysis to achieve a normal distribution. Differences in obese (BMI ≥ 30) and nonobese (BMI<30) patients were analysed using unpaired t-tests, chi-squared analyses and nonparametric tests, wherever appropriate. Uni- and multivariate regression analysis (with age, sex, atopy, FEV_1 and oral corticosteroid dose as independent factors) was used to assess associations between BMI and parameters of lung function (FEV_1, FRC/TLC) and airway inflammation (blood and sputum eosinophils and neutrophils, FeNO, PC_{20} histamine and hs-CRP). The regression line was described by the correlation coefficient (r) and the slope of the regression line (B). Logistic regression analysis was performed to determine whether there was an association between the presence of obesity (independent factor) and the presence of each of the five co-morbid factors (dependent factor). Odds ratios (OR) with 95% confidence intervals (CI) were obtained. All analyses were performed using the Statistical Package of the Social Sciences (SPSS version 12.0). P-values less than 0.05 were considered statistically significant.

Results

Comparison between obese and nonobese patients

Obese patients (BMI ≥ 30, n=29) did not differ from those with BMI <30 (n=107) with respect to age, atopy, age of asthma onset and medication dose. There was a trend (p=0.06) for a longer duration of asthma in the obese patients. Obese patients had a higher FEV_1 %pred than nonobese patients and a lower FRC/TLC %pred (Table 1). Patients with a high BMI (≥ 30) had a lower percentage of sputum eosinophils and sputum neutrophils and lower FeNO values as compared to patients with BMI <30. Hs-CRP was higher in obese as compared with nonobese patients. There was no difference in blood eosinophils or airway responsiveness between the two groups (Table 2).

Table 1. Clinical and lung function characteristics in obese *vs.* nonobese patients.

	BMI <30 (n=107)	BMI ≥30 (n=29)	p-value
Age (y)	44.8 (15.0)	47.4 (11.4)	0.39
Sex (%female)	68.2	75.9	0.43
Age of asthma onset* (y)	17.5 (0.5-68)	8.0 (0.5-54)	0.37
Asthma duration*(y)	17 (2-73)	27 (6-57)	0.06
Ex-smoker (%)	36.4	48.3	0.25
Atopy (%)	55.8	65.5	0.35
Inhaled steroids (µg/day)*	1600 (1600-6400)	1600 (1600-4000)	0.88
Daily oral steroids (%)	33	31	0.84
FEV_1 %pred	75.8 (24.3)	85.9 (23.0)	0.05
FEV_1/VC % pred	79.1 (20.0)	84.9 (17.6)	0.17
FRC/TLC %pred	117.7 (31.0)	100.3 (25.6)	0.009
BMI*	24.4 (17.5-29.9)	32.7 (30.1-44.9)	< 0.001

BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC forced vital capacity; FRC, functional residual capacity; TLC, total lung capacity. Data in mean (sd) or *median (range) or percentage of patients having the factor. %pred denotes percentage of the predicted value.

Table 2. Inflammatory characteristics in obese *vs.* nonobese patients.

	BMI <30 (n=107)	BMI ≥30 (n=29)	p-value
Blood eosinophils ($x10^9$/L)	0.21 (0-1.35)	0.15 (0.01-0.83)	0.13
Sputum eosinophils (%)	2.8 (0-59.4)	0.5 (0-12.4)	0.03
Sputum neutrophils (%)	72.0 (11.6-97.4)	54.6 (33.5-94.8)	0.01
FeNO (ppb)	11.1 (2-202.3)	7.2 (2-35.3)	0.03
PC_{20} histamine (mg/ml)	1.31 (0.02-8)	1.91 (0.02-8)	0.64
hs-CRP (mg/L)	2.5 (0.5-65.3)	8.1 (0.5-33.7)	0.003

BMI, body mass index; FeNO, exhaled nitric oxide; PC_{20} , provocative concentration to cause a 20% fall in FEV_1; hs-CRP, high sensitivity CRP. Data in median(range).

Obese patients had a higher total number of co-morbid factors as compared with nonobese patients (median (range): 3(1-4) vs. 2(0-4), p<0.01). Of the five investigated co-morbid factors, gastroesophageal reflux and obstructive sleep apnoea were more prevalent among the obese patients as compared with the nonobese patients (Table 3). Although the percentage of patients with psychopathology was not significantly different between both groups, obese patients had higher overall GHQ scores than nonobese patients (median(range):3.0 (0-12) vs. 1.0 (0-12), p=0.03).

Association between obesity and parameters of asthma severity

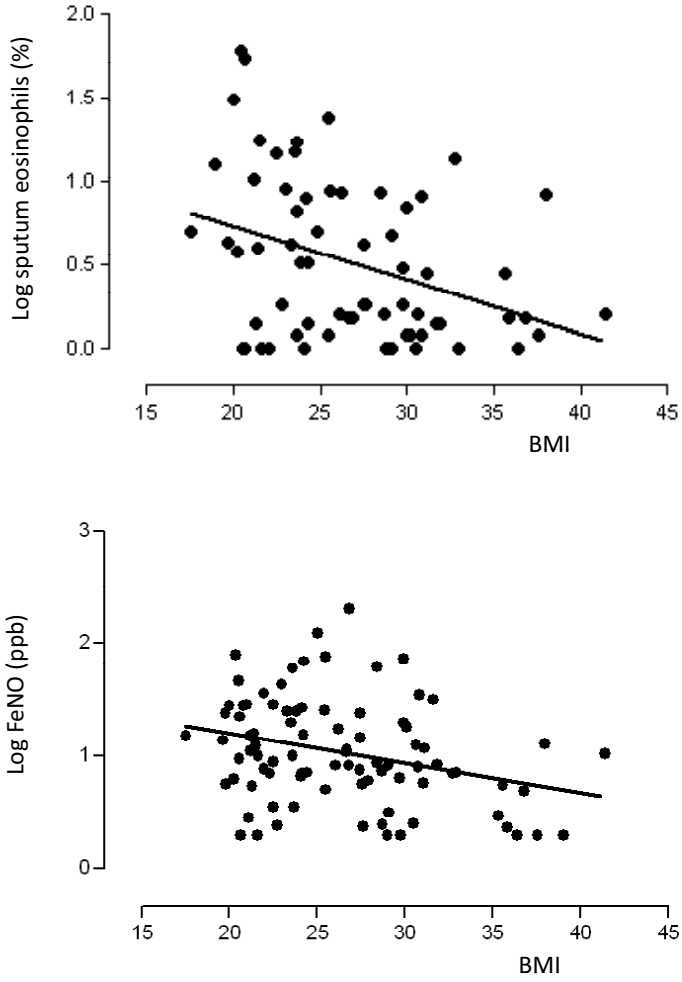
Linear regression analysis showed a negative association between BMI and sputum eosinophils (r= -0.36, B= -0.03, p= 0.003) and BMI and FeNO (r= -0.30, B= -0.03, p= 0.005) (Figure 1). These associations remained in the multivariate regression analysis after adjustment for age, sex, atopy, FEV_1 and oral corticosteroid dose (r= -0.40, B= -0.03, p= 0.02 and r= -0.33, B= -0.03, p= 0.01 respectively). Multivariate regression analysis including the same co-variates showed a positive association between BMI and hs-CRP (r= 0.50, B= 0.42, p< 0.01) and a negative association between BMI and FRC/TLC (r=- 0.84, B= -1.3, p <0.01). Logistic regression analysis showed that obese patients had a 2.3-fold (CI: 1.0-5.5) increased risk for gastroesophageal reflux and a 3.1-fold (1.1-9.0) increased risk for sleep apnoea (Figure 2).

Table 3. Co-morbid factors in obese *vs.* nonobese patients.

	BMI <30 (n=107)	BMI ≥ 30 (n=29)	p-value
Severe chronic sinus disease (%)	37.5	36.8	0.96
Gastroesophageal reflux (%)	44.9	65.5	0.05
Recurrent respiratory tract infections (%)	55.1	69.0	0.18
Psychopathology (%)	16.9	32.0	0.10
Obstructive sleep apnoea (%)	9.3	24.1	0.05

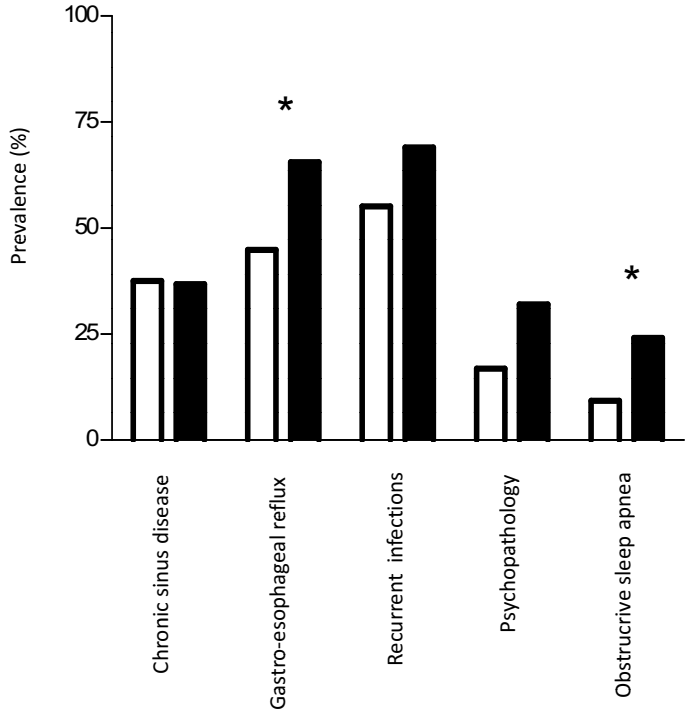
BMI, body mass index. Data in percentage of patients having the factor.

Figure 1. Relationship between BMI and inflammatory parameters: sputum eosinophils and exhaled nitric oxide.



Upper panel: r=-0.36, B=-0.03, P=0.003; lower panel: r=-0.30, B=-0.03, p=0.005

Figure 2. Prevalence of co-morbid factors.



Obese (n=29, black bars) vs. non-obese (n=107, white bars) patients. *p<0.05

Discussion

In this study, obesity in patients with difficult-to-treat asthma was not associated with more severe airway inflammation or more airway obstruction, but was related to reduced lung volume and to the presence of aggravating co-morbid factors. Body mass index was negatively associated with sputum eosinophils and exhaled nitric oxide, and obese patients had an increased risk of gastroesophageal reflux (2.3 fold) and obstructive sleep apnoea (3.1 fold). These results suggest that obese patients with difficult-to-treat asthma represent a group of patients that may require a specific treatment approach.

The negative association between BMI and sputum eosinophils and FeNO is in contrast with previous findings in a population-based cohort where no relation was found between obesity and FeNO (20). Interestingly, a short communication describing a group of patients with mild asthma also showed a negative association between BMI and FeNO (21) which

supports our findings in difficult-to-treat asthmatic patients. Our study also shows that obese patients with difficult to treat asthma had more co-morbid factors than nonobese patients, in particular gastroesophageal reflux and sleep apnoea. Obesity has been related with a higher prevalence of several co-morbid factors in the general population (22-24) and the presence of co-morbid factors has been related to more severe asthma (12;25;26). This study extends these findings by linking obesity to co-morbid factors in patients with difficult-to-treat asthma. In the present study, there was a trend for a longer asthma duration in the obese patients as compared with the nonobese. A previous study in persistent asthma did not find a difference in asthma duration between overweight patients and those with normal BMI (4). It might be possible that in our study group life long asthma and prolonged use of corticosteroids have contributed to the development of obesity. Taken together, a low level of airway inflammation and the presence of aggravating co-morbid factors seem to characterize the obese patient with difficult-to-treat asthma.

We do not think that the results of our study are influenced by selection bias or inadequate methodology. All patients, obese as well as nonobese, fulfilled the same strict selection criteria for difficult-to-treat asthma (9). They had a firm diagnosis of asthma, based on a history of episodic dyspnoea and wheezing, hyperresponsiveness to inhaled histamine (PC_{20} < 8mg/ml), and/or a documented bronchodilator reversibility in FEV_1 >12% predicted. They were symptomatic despite the use of high doses of asthma medication, and had experienced a severe asthma exacerbation during the year before entering the study. Airway inflammation was measured by cell differential counts in induced sputum and the level of nitric oxide in exhaled air. These measurements are now widely accepted as reliable noninvasive tools to assess airway inflammation in asthma (27;28). One could argue that adherence to oral corticosteroids might have influenced our results, since adherent patients are likely to have less airway inflammation and a higher BMI. However, we do not believe that this was an important confounding factor, because oral steroid dependent patients only represented one third of the total group, and the association between obesity and airway inflammatory markers remained significant after adjustment for oral corticosteroid dose.

Our finding of less severe airway inflammation in obese patients with asthma may be unexpected. Several studies have demonstrated persistent low-grade systemic inflammation in obese individuals compared to lean subjects as indicated by higher circulating levels of amyloid A, fibrinogen, tumour necrosis factor alpha and CRP. Also in our study, CRP levels were increased in the obese patients. It has been suggested that high levels of pro-inflammatory molecules released from adipose tissue into the systemic circulation could contribute to airway inflammation, thereby increasing the prevalence and severity of asthma in the obese (29). Although cross-sectional and prospective cohort studies in humans have

indeed demonstrated a modest overall increase in asthma prevalence and severity in the obese, our results do not support the hypothesis that this is caused by enhanced airway inflammation. Our study rather suggests that altered lung volumes and a higher prevalence of co-morbid factors are the mechanism whereby obesity contributes to increased asthma severity. A decrease in functional residual capacity as observed in the obese patients in our study not only causes shallow breathing and increased dyspnoea sensation, but might also enhance airway responsiveness by unloading of the airway smooth muscle. Furthermore, an increased prevalence of obesity related co-morbid factors, such as gastroesophageal reflux and sleep apnoea are also likely to contribute to more severe asthma symptoms.

Our study has pathophysiological and clinical implications. It shows that low grade systemic inflammation as observed in obese patients is not necessarily associated with enhanced airway inflammation. The finding of less severe airway inflammation in the obese patients suggests that their underlying asthma may in fact be milder. This raises the hypothesis that the effects of the adipose tissue on lung function or the presence of co-morbid factors make them more symptomatic and difficult to treat. If so, weight reduction in obese patients might improve asthma control by reducing the impact of co-morbid factors and by attenuating the negative effects on lung volumes. Studies have indeed shown that weight reduction programmes reduce symptoms in patients with asthma (30).

In conclusion, our study has shed new light on the association between obesity and asthma severity. Obese patients with difficult-to-treat asthma do not have more airway inflammation as compared with nonobese patients. On the contrary, they have higher FEV_1 and less airway inflammation. The results of our study fit in with the hypothesis that obese patients with asthma may exhibit more severe asthma symptoms or even become difficult-to-treat because of an unfavorable effect of overweight on lung function, or because of aggravating co-morbid factors including gastroesophageal reflux and obstructive sleep apnoea. The therapeutic approach of obese patients with difficult-to-treat asthma should therefore not be primarily focused on intensifying anti-inflammatory treatment but rather on weight reduction and adequate control of co-morbid factors.

References

(1) Ford ES. The epidemiology of obesity and asthma. J Allergy Clin Immunol 2005; 115(5):897-909.

(2) Beuther DA, Sutherland ER. Overweight, Obesity and Incident Asthma: A Meta-analysis of Prospective Epidemiologic Studies. Am J Respir Crit Care Med 2007.

(3) Shore SA. Obesity and asthma: implications for treatment. Curr Opin Pulm Med 2007; 13(1):56-62.

(4) Saint-Pierre P, Bourdin A, Chanez P, Daures JP, Godard P. Are overweight asthmatics more difficult to control? Allergy 2006; 61(1):79-84.

(5) 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):334-339.

(6) The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. Eur Respir J 2003 Sep ;22 (3):470-477.

(7) Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. Am J Respir Crit Care Med 2006; 174(2):112-119.

(8) Shore SA, Fredberg JJ. Obesity, smooth muscle, and airway hyperresponsiveness. J Allergy Clin Immunol 2005; 115(5):925-927.

(9) Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. Eur Respir J 1999; 13(5):1198-1208.

(10) ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. Factors associated with persistent airflow limitation in severe asthma. Am J Respir Crit Care Med 2001 Sep 1;164 (5):744 -748.

(11) ten Brinke A, van Dissel JT, Sterk PJ, Zwinderman AH, Rabe KF, Bel EH. Persistent airflow limitation in adult-onset nonatopic asthma is associated with serologic evidence of Chlamydia pneumoniae infection. J Allergy Clin Immunol 2001 Mar ;107 (3):449 -454.

(12) ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2005; 26(5):812-818.

(13) 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.

(14) ten Brinke A, de Lange C, Zwinderman AH, Rabe KF, Sterk PJ, Bel EH. Sputum Induction in Severe Asthma by a Standardized Protocol. Predictors of excessive bronchoconstriction. Am J Respir Crit Care Med 2001 Sep 1;164 (5):749 -753.

(15) 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):912-930.

(16) Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O'Byrne PM, Anderson SD et al. 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.

(17) Masclee AA, de Best AC, de Graaf R, Cluysenaer OJ, Jansen JB. Ambulatory 24-hour pH-metry in the diagnosis of gastroesophageal reflux disease. Determination of criteria and relation to endoscopy. Scand J Gastroenterol 1990; 25(3):225-230.

(18) Goldberg DP. The detection of psychiatric ilness by questionnaire. London: Oxford University Press, 1972.

(19) Stradling JR, Davies RJ. Sleep. 1: Obstructive sleep apnoea/hypopnoea syndrome: definitions, epidemiology, and natural history. Thorax 2004; 59(1):73-78.

(20) McLachlan CR, Poulton R, Car G, Cowan J, Filsell S, Greene JM et al. Adiposity, asthma, and airway inflammation. J Allergy Clin Immunol 2007; 119(3):634-639.

(21) Barros R, Moreira A, Fonseca J, Moreira P, Fernandes L, de Oliveira JF et al. Obesity and airway inflammation in asthma. J Allergy Clin Immunol 2006; 117(6):1501-1502.

(22) Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA, Jr. Body-mass index and symptoms of gastroesophageal reflux in women. N Engl J Med 2006; 354(22):2340-2348.

(23) Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G et al. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry 2006; 63(7):824-830.

(24) Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med 2002; 162(8):893-900.

(25) Kasasbeh A, Kasasbeh E, Krishnaswamy G. Potential mechanisms connecting asthma, esophageal reflux, and obesity/sleep apnea complex-A hypothetical review. Sleep Med Rev 2007; 11(1):47-58.

(26) Sontag SJ, O'Connell S, Miller TQ, Bernsen M, Seidel J. Asthmatics have more nocturnal gasping and reflux symptoms than nonasthmatics, and they are related to bedtime eating. Am J Gastroenterol 2004; 99(5):789-796.

(27) Taylor DR. Nitric oxide as a clinical guide for asthma management. J Allergy Clin Immunol 2006; 117(2):259-262.

(28) Brightling CE. Clinical applications of induced sputum. Chest 2006; 129(5):1344-1348.

(29) Shore SA, Johnston RA. Obesity and asthma. Pharmacol Ther 2006; 110(1):83-102.

(30) Simard B, Turcotte H, Marceau P, Biron S, Hould FS, Lebel S et al. Asthma and sleep apnea in patients with morbid obesity: outcome after bariatric surgery. Obes Surg 2004; 14(10):1381-1388.