RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

RC-02202_R1

Obesity and Asthma: Impact on severity, asthma control and response to therapy

Caroline Trunk-Black Juel MD & Charlotte Suppli Ulrik MD DMSc

Dept. of Pulmonary Medicine, Hvidovre Hospital & University of Copenhagen, Hvidovre, Denmark

Key words: Asthma, obesity, asthma control, quality of life, response to therapy

Correspondence:
Charlotte Suppli Ulrik
Virum Overdrevsvej 13
DK-2830 Virum
Denmark
csulrik@dadlnet.dk

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

Abstract

Asthma is more prevalent in obese compared with normal weight subjects. Our aim has been to review current knowledge of the impact of obesity on asthma severity, asthma control, and response to therapy.

Several studies have shown that overweight and obesity is associated with more severe asthma and impaired quality of life compared with normal weight individuals. Furthermore, obesity is associated with poorer asthma control, as assessed by asthma control questionnaires, limitations in daily activities, breathlessness and wheezing, use of rescue medication, unscheduled doctor visits, emergency department visits, and hospitalizations for acute asthma. Studies of the impact of a high body mass index (BMI) on response to asthma therapy have, however, revealed conflicting results. Most studies show that overweight and obesity is associated with less favorable response to asthma therapy with regard to symptoms, level of FEV_1, fraction of exhaled nitric oxide, and airway responsiveness. Some studies suggest that asthma in the obese patient might be more responsive to leukotriene modifiers, orchestrated by leptin and/or adiponectin derived from adipose tissue, than to inhaled corticosteroids, possibly reflecting differences in the underlying airway inflammation in obese vs. non-obese asthmatics.

In conclusion, overweight and obesity is associated with poorer asthma control and, very importantly, overall poorer response to asthma therapy compared with normal weight individuals.

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

Introduction

Overweight and obesity is associated with a number of well-known health hazards, including diabetes and cardiovascular disease (1). Furthermore, evidence from recent years suggests that obesity is also a risk factor for asthma (2). According to the World Health Organization (WHO), the worldwide prevalence of obesity nearly doubled from 1980 to 2008 (3), and likewise a dramatic increase in the reported prevalence of asthma has been observed in recent decades (4).

Many prospective studies show that obesity is a risk factor for asthma and have found a positive correlation between increase in Body Mass Index (BMI) and subsequent development of asthma. Obesity can reduce lung compliance, lung volumes and disturb the ventilation-perfusion relationship. Furthermore, obesity leads to higher levels of hormones produced in adipose tissue, of which some are pro-inflammatory. This systemic pro-inflammatory state might worsen the airway inflammation seen in asthmatic patients. The question is, therefore, what is the probable link between obesity and asthma? And not least, does obesity have an impact on the clinical manifestations of asthma, including response to therapy.

The aim of the present paper is to provide an overview of our current knowledge of the impact of overweight and obesity on the clinical manifestations of asthma, including asthma control and response to therapy.

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

Methods

A series of systematic searches were carried out, last updated October 2012, using the database PubMed. The strategy was intended to be broad in order to maximize the capture of citations for peer-reviewed publications relevant to asthma and obesity. The PubMed searches were carried out using the following algorithm of MeSH terms: Asthma, asthma control, asthma management, asthma severity or asthma-like symptoms AND obesity or overweight, and the searches were repeated with these terms in combination with pathogenesis, therapy, and epidemiology. The citation pool was further supplemented from manual assessment of the reference lists accompanying other systematic reviews of aspects related to asthma in obese individuals and from other publications identified as being relevant for further review. The search was limited to English-language articles published after 1990; and only studies published in peer-reviewed journals were included in this systematic review. Studies published solely in abstract form were excluded because the methods and results could not be fully assessed.

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

Results

Obesity and Asthma Severity

In a retrospective review of medical records, Akerman et al. (5) investigated the relationship between obesity and asthma in 143 adults (113 females), of whom 72% were obese, and reported a linear relationship between asthma severity, defined according to the National Heart Lung and Blood Institute guidelines, and body mass index. Furthermore, females with asthma had significantly higher BMI compared with males with asthma. Based on data from the National Asthma Survey in the US, Taylor et al. (6) studied the association between body mass index and asthma severity in 3.095 adults with self-reported asthma. A total of 32% and 33%, respectively, of the sample were overweight and obese. Compared with non-overweight individuals, obese individuals with asthma were more likely to report persistent symptoms, more use of reliever medication, use of controller medication, and to be classified as having severe persistent asthma; and the authors therefore concluded that obesity is associated with several characteristics of more severe asthma.

Varrasso et al.(7) studied in 2005 the relationship between BMI and asthma severity by gender, information was gathered from 366 adults with well-characterised asthma taking part in the Epidemiological Study on the Genetics and Environments of Asthma (EGEA), a case control study to assess genetic, environmental risk factors and their interactions for asthma (8). Severity of asthma was assessed by three criteria: clinical asthma severity score in previous year, hospitalisation for asthma ever and treatment with inhaled corticosteroids in previous year. The authors reported that an increase in asthma severity was significantly correlated with increasing BMI in women, but not in men. This association persisted after adjusting for confounders such as age, FEV_1 % predicted, smoking habits, BMI adjusted dyspnea, and the prevalence of asthma in first-degree relatives. Furthermore, the study also

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

revealed that the association between BMI and asthma severity was strongest among women with early menarche. In line with these findings, Lavoie et al. (9) reported that higher BMI is associated with higher Asthma Control Questionnaire (ACQ) scores and lower Asthma Quality of Life Questionnaire (AQLQ) scores (10).

In 2006, Mansell et al. (11) investigated whether linkage between airway hyperresponsiveness and obesity could at least partly explain the prevalence of obesity in asthmatic adolescents. A total of 216 adolescents aged 12-18 were divided into three groups: Probands (n=55) with one or more previous episodes of acute severe asthma, a control group (n=79) with at least mild persistent asthma, and a group (n=82) of healthy subjects. Mean values of BMI were found to be significantly higher among the 134 adolescents with asthma compared with the group of healthy adolescents. Among the patients with asthma, 42% were found to be at risk of overweight, and 25% to be overweight, compared with 29% and 16%, respectively, among the non-asthmatic controls. No relationship was found between total lung capacity (TLC) and BMI, or asthma status. Bronchial challenge testing with methacholine showed, as expected, airway hyperresponsiveness, defined as a PC_{20} $FEV_1 \leq 10$ mg/ml, more often in patients with asthma compared to non-asthmatic subjects, but no significant association was observed between dynamic hyperinflation during positive challenges and overweight vs. non-overweight status. Furthermore, no significant differences were observed between weight groups in overall asthma severity score, defined according to Global Initiative for Asthma (GINA) guidelines (12), or use of controller medication, whereas overweight subjects had greater decreases in inspiratory flows. The authors concluded that overweight in adolescents is associated with baseline airflow limitation, but not airway responsiveness.

Peters et al (13) performed a 12-month randomized controlled trial comparing disease management with traditional care in 902 patients (473 children and 429 adults). The

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

prevalence of overweight/obesity was 45% and 58%, respectively, among children and adults, and the relationship between BMI, asthma severity, spirometry findings, health care utilization (HCU) and quality of life (QOL) was analyzed. The QOL was assessed using the pediatric and adult versions of the AQLQ and the 36-item Short Form Health Survey. Information on all HCU was obtained by patient interviews and extensive medical record review. No association was observed between obesity and asthma severity, spirometry findings, QOL, or HCU in children, whereas in adult asthmatics obesity was associated with lower FVC and QOL, but not with asthma severity or HCU.

Obesity and Asthma Control

Lavoie et al. (9) evaluated the associations between BMI and levels of asthma severity, asthma control, and asthma-related quality of life in 382 adult outpatients with asthma, of whom 39% and 25%, respectively, were overweight and obese. Patients with higher BMI scored higher on the Asthma Control Questionnaire (ACQ), independent of age, gender, and asthma severity defined by GINA guidelines (12). There were significant associations between individual items on the ACQ, showing that patients with higher BMI had more early morning symptoms, greater limitation in daily activities, more shortness of breath and wheezing, and more need for rescue medication. Likewise, higher BMI was also associated with lower scores on Asthma Quality of Life Questionnaire (AQLQ). Further analyses revealed that with increasing BMI, the decline in asthma-related quality of life, including activity limitations, were more pronounced in men compared to women.

Peters-Golden et al. (14) conducted a post hoc analysis assessing the possible influence of BMI on the response to asthma controller medication of data from a randomised, controlled trial comprising 3037 adults with moderate asthma allocated to either montelukast,

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

beclomethasone or placebo. The primary end point in the analysis was asthma control days (ACD, defined as days with max. two puffs of reliever medication, no night time awakening, and no asthma attacks). The analysis of data for patients on placebo revealed that normal-weight subjects had higher percentage of Asthma Control Days (34%) compared with patients who were overweight (25%) or obese (26%).

In another study, also from 2006, Dixon et al. (15) studied the effect of obesity on clinical presentation of asthma and response to therapy in a cohort of 488 (47% obese) subjects with mild to moderate persistent asthma. No difference was observed in cough, wheeze or shortness of breath between the normal weight, overweight and obese, whereas they found indications of poorer asthma control in the obese group, as assessed by ACQ score and use of rescue medication.

Saint-Pierre et al. (16) carried out a longitudinal follow-up study of 406 outpatients with persistent asthma. Patient characteristics were described as a function of BMI <25 (260 patients, 160 women), >25 (146 patients, 72 women) and as a function of asthma severity. Asthma control and severity was evaluated according to GINA guidelines (12); and asthma control classified as acceptable or unacceptable. A clear relationship was found between BMI and severity with more overweight patients in the severe asthma group. Furthermore, daily dose of oral corticosteroid (OCS) and the total dose of OCS during the previous year (< 2g r or > 2gr) were also positively correlated with BMI. The transition unacceptable to acceptable asthma control was, after adjustment for covariates associated with BMI, less common in overweight patients. On the other hand, the reverse transition from acceptable to unacceptable asthma control state was not significantly associated with BMI.

In 2010 Kattan et al.(17) studied the relationship between adiposity, gender and asthma control in a group of 368 inner-city adolescents with asthma (169 females, of whom 60% and

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

36%, respectively, had BMI > 85th and 95th percentile of BMI for age; 199 males, of whom 50% and 33%, respectively, had BMI > 85th and 95th percentile of BMI for age. The analysis revealed that adiposity was related to poorer asthma control, as assessed by the Asthma Control Test (ACT) in female subjects, but not in males.

Further studies by Rodrigo et al. 2007 (18), and Taylor et al. (19) found hospitalization rates to be higher among obese patients with asthma compared to under/normal weight subjects with asthma. In keeping with this, Taylor et al. (19) also found the rate of unscheduled doctor visits to be higher among obese individuals with asthma. A significant difference was also found between duration of stay at the emergency room (ER) (2.3 h vs. 1.9 h, respectively) and discharge rate after initial treatment at the ER (13.7% vs. 6.8%, respectively) between overweight/obese and normal weight patients with asthma.

In a recent smaller study by Kilic et al. (20) the effects of obesity on asthma control was evaluated in 41 obese women with asthma and 40 non-obese women with asthma recruited from an out-patient clinic. Asthma was diagnosed according to the GINA guidelines (12), and asthma severity was also classified according to GINA guidelines (12). Data on serum leptin levels, fraction of exhaled nitric oxide (F_ENO), asthma control (assessed by the ACT) and presence of atopy were obtained, and the relationship between these parameters and BMI were compared in the two groups. Uncontrolled asthma was found in 61% of the women in the obese group compared to only 38% of those in the non-obese group, mean leptin-levels was significantly higher in obese patients with asthma, but no correlation was found between BMI and F_ENO levels. The authors concluded that obesity is an important risk factor for uncontrolled asthma.

In a retrospective study, Quinto et al. (21) studied the impact of overweight and obesity on asthma control. A cohort of 32.321 children, aged 5-17 years and treated with at least one

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

asthma medication (controller or rescue), were enrolled. The study showed that overweight (BMI percentile for age, 85% to 94%) and obese (BMI percentile for age ≥ 95%) children were more likely to have a higher amount of β-agonists dispensed. Furthermore, over-weight and obese children also had an increased risk of being prescribed rescue prednisolone, odds ratio of 1.21 (95% CI, 1.13-1.29) and odds ratio of 1.28 (95% CI, 1.21-1.36), respectively, compared with children with normal weight (BMI percentile for age, 16-84%). The significant association between childhood obesity and worse asthma control and exacerbations persisted after adjusting for demographics, parental education level, asthma controller use, gastro-oesophageal reflux disease and diabetes mellitus.

On the other hand, Clerisme-Beaty et al. (22) performed a cross sectional assessment of asthma control in 292 patients with asthma, the majority were women (82%) and African-American (63%), recruited from primary care using four different validated survey tools, the Asthma Control and Communication Instrument (ACCI), the ACT, the ACQ and the Asthma Therapy Assessment Questionnaire (ATAQ). A high prevalence of obesity (63%) was found, but regression analysis showed no association between obesity or increasing BMI level and asthma control as assessed by the four questionnaires. These observations persisted after adjusting for confounders such as FEV_1, smoking status, ethnicity, gender, selected comorbid illness and long-term use of asthma controller medication. Furthermore, no differences were found in asthma-related acute health care use or prescribed asthma medications by BMI categories.

In a study from Spain, Sastre et al. (23) investigated the association between body mass index and asthma control in a large sample of patients with asthma. Data was obtained from a previous study in which different Asthma Control Questionnaires (ACQ) – ACQ-FEV1, ACQ-peak expiratory flow, and ACQ without lung function – and the Asthma Control Test (ACT)

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

were validated in a Spanish cohort comprising 607 adults with asthma (61% female), of whom more than 36% were found to be overweight or obese. No significant association was observed between BMI and asthma control as defined by physicians or according to the ACT or ACQ scores. The percentage of patients with poor asthma control was slightly higher in participants with both low BMI (BMI<18.5) and obesity (BMI>30).

For obvious reasons, the findings in the two latter studies lead the authors to question the relation between obesity and asthma. However, the lack of association may be due to differences in measures of asthma control or characteristics of the studied cohorts, including proportion of obese individuals and females.

Obesity and Response to Asthma Therapy

Peters-Golden et al. (14) conducted a study of 3037 patient evaluating the relationship between BMI and response to controller therapy with a leukotrien modifier (montelukast – 10 mg q.d. nocte) and inhaled corticosteroid (beclomethasone – 200 µg (four puffs) b.i.d.) in patients classified as having moderate asthma. The end-points were proportion of asthma control days (ACD as defined above) and percentage change from baseline in $FEV_{1,}$ night-time awakenings and use of rescue medication. Their study showed that the efficacy of the two therapies by BMI category, as assessed by mean placebo-adjusted percentage ACD was significantly greater for beclomethasone than for montelukast in patients with normal BMI (18.6 versus 9.5%, respectively). However, this difference between treatment groups was statistically insignificant among overweight patients (18.8 versus 15.7%, respectively) and next to none among obese patients (13.9 versus 13.4%, respectively). The number of night-time awakenings was higher among overweight and obese patients, compared with normal weight participants, for both treatments. No statistically significant differences were found in

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

use of rescue medication or percentage change in FEV_1 from baseline across the different BMI groups for any of the treatment groups. Based on their findings, the authors speculated whether asthma in the overweight and the obese may be a more leukotriene-driven type of asthma compared with asthma in normal weight individuals, and by that, whether controller medication including a leukotriene modifier could be beneficial for overweight and obese patients with asthma.

In keeping with this, Giouleka et al. (24) conducted a relatively small study to determine whether obesity influences asthmatic airway inflammation, and whether the hormones leptin or/and adiponectin, produced in adipose tissue and regulating several metabolic and inflammatory pathways, contribute to a possible link between asthma-related and obesity-related inflammation. Their study comprised 100 patients with asthma and 60 healthy controls. Obesity was found to be associated with increased urinary leukotriene levels, supporting the theory that alterations of leptin/adiponectin balance may be related to the presence of leukotriene inflammation in obese patients with asthma. Kilic et al. (20) have also reported serum leptin levels to be significantly higher in obese patients with asthma compared with non-obese patients with asthma.

Anderson and Lipworth (25) have recently studied the effect of BMI on response to inhaled budesonide in 72 patients with mild to moderate persistent asthma divided into two groups, overweight (BMI>25) and normal weight (BMI<25) participants. Each group received two 4-week treatment periods with inhaled budesonide 200μg/day and 800μg/day, and separated by a wash-out period. Outcome variables included FEV_1, F_ENO, airway responsiveness assessed as methacholine PC_{20}, total daily asthma symptom score, and overnight urinary cortisol/creatinine ratio. The study revealed that overweight patients with persistent asthma appears to have less symptom and F_ENO response to inhaled budesonide, whereas no

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

differences were found in FEV_1 or airway responsiveness to methacholine between the overweight and normal weight group. In line with this, Sutherland et al. (26) found elevated BMI to be associated with reduced in vitro response to dexamethasone in overweight and obese patients.

In a more recent study, Sutherland et al. (27) explored whether increasing BMI influenced responses to treatment with inhaled fluticasone dipropionate and oral montelukast in patients with persistent asthma. A total of 1052 subjects, divided into categories according to weight (underweight, normal weight, overweight and obese), were enrolled in a double-blind, randomized, parallel-group trial of 12-weeks duration comparing fluticasone and montelukast. This study showed, in contrast to the findings by Peters-Golden et al. (14), that fluticasone compared to montelukast leads to greater symptom reduction within all weight groups. They also found a statistically greater improvement in FEV_1 % predicted in all weight groups treated with fluticasone.

Furthermore, Camargo et al. (28) studied the relationship between BMI and response to treatment with fluticasone propionate plus salmeterol (discus 100/50 μg) vs. montelukast (10mg) in a retrospective analysis of four previously published clinical trials. Enrolled patients were classified according to BMI as underweight (<20), normal weight (20-25), over-weight (25-30), obese-1(30-35), obese-2(35-40), and obese-3 (≥40). Out-come measures included FEV_1, asthma symptom score, and use of rescue albuterol. The study showed that compared to subjects with normal BMI, the time to peak FEV_1 seems to be longer in the very obese patients, and that treatment responses to fluticasone/salmeterol were consistently greater compared to montelukast, also at high BMI levels.

In an analysis of pooled data from five recently published studies, Boulet et al. (29) studied the relationship between body mass index and the response to fluticasone propionate (ICS),

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

with (50/100 μg) or without (100 μg) the long-acting β_2-agonist salmeterol. A total of 1242 individuals were included in the analysis, and asthma control was defined by GINA guidelines (12). The analyses showed that in both the obese and the non-obese group of patients, the combination of fluticasone and salmeterol was more effective in terms of asthma control than fluticasone alone. The analysis also revealed that the likelihood of achieving well-controlled asthma were significantly lower in obese subjects, particularly in individuals with a BMI ≥ 40. The majority of patients with uncontrolled asthma had diurnal and/or nocturnal asthma symptoms and was also more likely to have daily use of rescue bronchodilators. Furthermore, obese patients also had an increase in daily symptoms over 24h and an increase in bronchodilator reversibility.

Based on the Study of the Effectiveness of Low Dose Theophylline as Add-On therapy in Poorly Controlled Asthma" (LODO) trial, Dixon et al. (15) studied 488 patients with mild to moderate persistent asthma, all sub-optimally controlled on their current therapy as defined by a score >1,5 on ACQ (30). Patients were categorised according to BMI as normal-weight, overweight and obese. The study showed an increased exacerbation rate in obese patients on theophylline compared to those on placebo (8.1 versus 4.8 events per year), and the relative risk for an exacerbation associated with obesity among patients on theophylline (N=150) was 3.7 (95% CI 2.2 to 6.3, p<0,001). No significant difference in exacerbation rate was observed between non-obese and obese assigned to montelukast or placebo.

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

Discussion

Currently available published studies clearly show that obese patients with asthma have more severe asthma symptoms, poorer asthma control, and, furthermore, a less favorable response to asthma therapy as assessed by symptoms. Furthermore, symptoms such as early morning symptoms, shortness of breath and wheezing, night time wakening and limitation of daily activities are more prevalent and persistent in obese subjects suffering from asthma. Furthermore, greater use of rescue medication, primarily fast-acting β_2-agonist, has been observed among the overweight and obese individuals compared with normal weight individuals with asthma. In line with this, and perhaps even more important, is the observation that obese individuals with asthma have a higher rate of hospitalization for acute asthma and unscheduled doctor visits, and lower quality of life, as assessed by quality of life questionnaires, compared with normal weight individuals with asthma.

Whether the above mentioned findings are direct consequences of asthma or a result of the mechanical stress that obesity puts on our respiratory system may be questioned. Some researchers have suggested that obesity leads to a pro-inflammatory state initiated by the cytokines produced in adipose-tissue, which in turn leads to asthma-like symptoms. And so if this is the case the less-favorable effect of asthma control might be due to the fact that the targeting of asthma control is wrong. In line with this, studies have revealed a poorer response to inhaled corticosteroids in obese asthmatics, which may be caused by differences in the mechanisms leading to asthma symptoms and clinical signs of asthma in obese and non-obese individuals, including the type of airway inflammation. Hopefully, future studies will provide us with further knowledge with regard to the complex interaction between obesity and asthma, and by that possibly define a distinct obese asthma phenotype. A clearly defined obese asthma phenotype may lead us to measures to improve the overall health of overweight

RESPIRATORY CARE Paper in Press. Published on December 11, 2012 as DOI: 10.4187/respcare.02202

or obese individuals presenting with asthma symptoms, not least by targeted pharmacological therapy. The clinical consequence of this may be that asthma in the years to come should be managed differently in obese and non-obese individuals.

In our review of studies we come across the difference in results between genders a few times. Varasso et al. (7) reported that an increase in asthma severity was significantly correlated with increasing BMI in women but not in men. Lavoie et al (9) found increasing BMI to have a negative effect on asthma related quality-of-life, and activity limitations, among men but not among women. Kattan M et al (17) found obesity to be related to poorer asthma control in females but not in men. Given the conflicting observations, valid conclusions may not be drawn at present with regard to the effect of the gender-obesity interaction on asthma control; and further studies addressing this issue is therefore clearly needed.

A number of studies have shown that overweight and obese individuals with asthma have significant improvements in asthma control, as assessed by symptoms, use of medication, level of lung function and hospitalizations for asthma, after weight loss. The combination of poorer asthma control and response to therapy in overweight and obese individuals with asthma and improvements in asthma control following weight loss should teach all of us, not only health care providers, but also health care policy makers, that prevention of overweight and obesity is of utmost importance, both at the individual level and with regard to use of health care resources.

In conclusion, obesity has substantial negative impact on most clinically relevant measures of asthma control and response to therapy; and although the complex interaction between obesity and asthma is only limited understood these findings clearly indicate that measures aimed at preventing overweight and obesity is likely to have significant on overall asthma morbidity.

References

1. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of obesity, diabetes and obesity-related health risk factors, 2001. JAMA 2003;289(1):76-79
2. Brumpton B, Langhammer A, Romunstad P, Chen Y, Mai XM. General and abdominal obesity and incident asthma in adults: The hunt study. Eur Respir J 2012 May 31.(Epub ahead of print)
3. http://www.who.int/mediacentre/factsheets/fs311/en/index.html
4. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. Allergy 2004; 59(5):469-478.
5. Akerman MJH, Calcanis CM, Madsen MK. Relationship between asthma severity and obesity. J Asthma 2004;41(5):521-526.
6. 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.
7. Varasso 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
8. Pin I, Siroux V, Cans C, Kauffmann F, Maccario J, Pison C, Dizier MH. Familial resemblance of asthma severity in the EGEA study. Am J Respir Crit Care Med 2002;165(2):185-9
9. Lavoie KL, Bacon SL, Labrecque M, Cartier, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. Respir Med 2006; 100(4): 648-657
10. Juniper EF, Guyatt GH, Ferrie PJ Griffith LE. Measuring quality of life in asthma. Am Rev Respir Dis 1993; 147(4):832-838.
11. Mansell AL, Walders N, Wamboldt MZ, Carter R, Steele DW, Devin JA, Monica TH, Miller AL, Wamboldt FS. Effect of body mass index on response to methacholine bronchial provocation in healthy and asthmatic adolescents. Pediatr Pulmonol 2006:41(5): 434-440.
12. Global Initiative for Asthma. Global Strategy for asthma management and prevention. Bethesda, MD: National Heart, Lung and Blood Institute/World Health Organization, National Institutes of Health; 2011. Available from http://www.ginasthma.com [accessed October 2012].
13. Peters JI, McKinney JM, Smith B, Wood P, Forkner E, Galbreath AD. Impact of obesity in asthma: evidence from a large prospective disease management study. Ann Allergy Asthma Immunol 2011;106(1):30-5
14. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index in the response to asthma controller agents. Eur Respir J 2006;27(3):495-503
15. Dixon AE, Shade DM, Cohen RI, Skloot GS, Holbrook JT, Smith LJ, Lima JJ, Allayee H, Irvin CG, Wise RA. Effect of Obesity on Clinical Presentation and Response to Treatment in Asthma. J Asthma 2006;43(7):553-558
16. Saint-Pierre P, Bourdin A, Chanez P, Daures JP, Godard P. Are overweight asthmatics more difficult to control? Allergy 2006;61(1):79-84.

17. Kattan M, Kumar R, Bloomberg GR, Mitchell HE, Calatroni A, Gergen PJ, Kercsmar CM, Visness CM, Matsui EC, Steinbach SF, Szefler SJ, Sorkness CA, Morgen WJ, Teach SJ, Gan VN. Asthma control, adiposity, and adipokines among inner city adolescents. J Allergy Clin Immunol 2010;125(3):584-592
18. Rodrigo GJ, Plaza V. Body Mass Index and Response to emergency Department Treatment in Adults with Severe Asthma Exacerbations: a prospective cohort study. Chest 2007;132(5):1513-1519
19. Taylor B, Manning D, Brown C, Crocker D, Swum-bah N, Holguin F. Body mass index and asthma severity in the national Asthma Survey. Thorax 2008;63(1):14-20
20. Kilic H, Oguzulgen IK, Bakir F, Turktas H. Asthma in Obese Women: Outcomes and factors involved. J Investig Allergol Clin Immunol 2011;21(4):290-296
21. Quinto KB, Zuraw BL, Poon KY, Chen W, Schatz M, Christiansen SC. The association of obesity and asthma severity and control in children. J Allergy Clin Immunol 2001;128(5):964-9.
22. 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):207-212
23. Sastre J, Olaguibel JM, López Viña A, Vega JM, del Pozo V, Picado C. Increased body mass index does not lead to a worsening of asthma control in a large adult asthmatic population in Spain. J Investig Allergol Clin Immunol 2010;20(7):551-557
24. Giouleka P, Papatheodorou G, Lyberopoulos P, Karakatsani A, Alchanatis M, Roussos C, Papiris S, Loukides S. Body mass index is associated with leukotriene inflammation in asthmatics. Eur J Clin Invest 2011;41(1):30-38.
25. Anderson WJ, Lipworth BJ. Does body mass index influence responsiveness to inhaled corticosteroids in persistent asthma? Ann Allergy Asthma Immunol 2012;108(4):237-242.
26. 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):682-687.
27. Sutherland ER, Camargo CA, Busse WW, Meltzer EO, Ortega HG, Yancey SW, Emmet AH, Stempel DA. Comparative effect of body mass index in response to asthma controller therapy. Allergy Asthma Proc 2010;31(1):20-25
28. Camargo CA Jr, Boulet LP, Sutherland ER, Busse WW, Yancey SW, Emmet AH, Ortega HG, Ferro TJ. Body mass index and response to asthma therapy: fluticasone propionate/salmeterol versus montelukast. J Asthma 2010;47(1):76-82.
29. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. Respir Med 2007;101(11):2240-7.
30. 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):902-907