

Njira L. Lugogo, Monica Kraft and Anne E. Dixon

J Appl Physiol 108:729-734, 2010. First published Oct 29, 2009; doi:10.1152/jappphysiol.00845.2009

You might find this additional information useful...

This article cites 76 articles, 29 of which you can access free at:

<http://jap.physiology.org/cgi/content/full/108/3/729#BIBL>

Updated information and services including high-resolution figures, can be found at:

<http://jap.physiology.org/cgi/content/full/108/3/729>

Additional material and information about *Journal of Applied Physiology* can be found at:

<http://www.the-aps.org/publications/jappl>

This information is current as of September 8, 2010 .

HIGHLIGHTED TOPIC | *Pulmonary Physiology and Pathophysiology of Obesity*

Does obesity produce a distinct asthma phenotype?

Njira L. Lugogo,¹ Monica Kraft,¹ and Anne E. Dixon²

¹Department of Medicine, Duke University, Durham, North Carolina; and ²Department of Medicine, University of Vermont/Fletcher Allen Health Care, Burlington, Vermont

Submitted 31 July 2009; accepted in final form 27 October 2009

Lugogo NL, Kraft M, Dixon AE. Does obesity produce a distinct asthma phenotype? *J Appl Physiol* 108: 729–734, 2010. First published October 29, 2009; doi:10.1152/jappphysiol.00845.2009.—Obesity and asthma prevalence have been increasing over the past decade. Epidemiological evidence demonstrates that obesity results in an increased risk of developing incident asthma. Even modest levels of increased weight increase asthma risk. Recently published data suggest that obese asthma patients may represent a distinct phenotype of asthma. Obese asthma patients demonstrate increased asthma severity, as indicated by increased exacerbations and decreased asthma control; however, they do not appear to have increased airway cellular inflammation. It seems likely that obesity does not contribute to asthma through conventional Th type 2-mediated inflammatory pathways but, rather, through separate mechanisms that are specific to the obese state. This may explain the variable responses of obese asthma patients to conventional asthma therapies, specifically, relative corticosteroid resistance. Small studies suggest improvements in the disease with weight loss in obese asthma patients, and other interventions to target asthma in obese individuals need to be investigated. Several postulated mechanisms for the occurrence of this distinct phenotype have been postulated: 1) the presence of comorbidities, such as gastroesophageal reflux disease and sleep disordered breathing, 2) systemic inflammation associated with obesity (with elevated levels of circulating cytokines, such as IL-6 and TNF- α), 3) increased oxidative stress, and 4) hormones of obesity, such as adiponectin, leptin, and resistin. Although the mechanisms underlying obesity in asthma require further investigation, obesity plays a major role in the asthma epidemic and likely results in a distinct phenotype of the disease.

weight loss; airway hyperreactivity; airway inflammation; adipokines; sleep disordered breathing; gastroesophageal reflux disease

THE OBESITY EPIDEMIC has been increasing for the past several decades, and there are no signs that the trend will change in the near future. According to the Centers for Disease Control National Health Interview Survey, 30% of adults >18 yr old are obese and ~68% of adults in the United States are obese or overweight. The incidence of obesity has almost doubled within the past 20 years (8). Asthma prevalence and incidence have also increased over the past decade, with current prevalence of ~5% in the US population. There has been increased interest in determining whether the increased prevalence of obesity has resulted in the increasing incidence of asthma.

More than 40 cross-sectional and case-control studies have reported on the relationship between obesity and asthma since the 1990s. Almost without exception, these studies describe an increased prevalence of asthma in obese and overweight individuals throughout the world. Although such studies cannot

address the direction of causality, several large epidemiological studies have reported an increased odds ratio (OR), or relative risk, of developing incident asthma in obese individuals [body mass index (BMI) >30] (3, 4, 7, 10, 27, 54, 58, 73), suggesting that obesity is a risk factor for the future development of asthma.

The etiology of this increased risk of developing asthma with increasing obesity is an area of active research. In addition to the recognition that obesity results in an increased occurrence of asthma, there is mounting evidence that obese asthma patients have a distinct phenotype of the disease with increased severity of illness and a variable response to conventional medical therapies compared with lean asthma patients. These differences are likely related to differences in the underlying pathophysiology of the disease, issues that are addressed in greater detail in this review.

CLINICAL CHARACTERISTICS OF THE OBESE ASTHMA PHENOTYPE

Severity of asthma in the obese individual. Asthma appears to be more severe in obese individuals. Reports using data

Address for reprint requests and other correspondence: A. E. Dixon, Pulmonary and Critical Care Medicine, Smith 147, Fletcher Allen Health Care & Univ. of Vermont College of Medicine, 110 Colchester Ave., Burlington, VT 05401 (e-mail: anne.dixon@uvm.edu).

initially collected from select groups of asthma patients have revealed conflicting data (12, 68, 75). However, studies that have enrolled a broad population of asthma patients have consistently found that asthma is less well controlled and more severe in the obese population. In a survey of health plan participants with a diagnosis of asthma, Mosen et al. (50) reported worse asthma control, as measured by a symptom-based questionnaire, and a much greater risk of hospitalization (OR 4.6) in obese than in normal-weight asthma patients. Using population-based data from the four-state portion of the National Asthma Survey, Taylor et al. (70) found worse asthma control and greater likelihood of severe persistent disease in obese than in normal-weight asthma patients. Also supporting the concept that asthma is more severe in obese individuals when population-based cohorts are studied, Wen et al. (76), using data from the Behavioral Risk Factor Surveillance System (a population-based telephone survey in the United States), found that obese asthma patients were more likely to report an asthma attack in the last year than nonobese individuals. On balance, these studies suggest that obese asthma patients tend to have worse asthma control and more severe disease than nonobese individuals.

Response to therapy in the obese asthma patient. The reasons for more severe asthma in obese individuals are likely to be multifactorial. One factor that may contribute to poor asthma control is altered response to medication: obese asthma patients appear to be less responsive than nonobese asthma patients to standard asthma medications, as outlined below.

Altered response to medications has been reported in a number of studies of the effect of obesity on the response to pharmacological interventions. This was first described by Peters-Golden et al. (56), who used pooled data from studies of the leukotriene antagonist montelukast. They found that the response to inhaled corticosteroids decreased with increasing BMI, whereas the response to leukotriene antagonists remained fairly stable over a range of BMIs. This reduced response to inhaled corticosteroids was also described by Boulet and Franssen (5), who used data pooled from five pharmaceutical company-sponsored studies of fluticasone and fluticasone-salmeterol combination therapy. They found that obese participants were less likely to achieve asthma control with pharmacological intervention (inhaled corticosteroid alone or the combination of an inhaled corticosteroid and a long-acting β -agonist). In a study from Uruguay, Rodrigo and Plaza (59) also found that obese asthma patients had reduced response to therapy (including systemic steroids and albuterol) in the Emergency Department, with a significantly reduced improvement in peak flow and a trend toward less improvement in forced expiratory volume in 1 s. This reduced response to therapy may have important implications, inasmuch as Rodrigo et al. found that overweight and obese individuals were more likely to be hospitalized for their asthma. Altered response to another controller therapy was also described in a retrospective analysis of a study of add-on therapy for poorly controlled asthma by Dixon et al. (12), who found worse asthma control in obese asthma patients treated chronically with theophylline than with placebo in addition to their baseline therapy.

The reasons for this reduced response to therapy are not known; however, Sutherland et al. (67) demonstrated in vitro steroid resistance when measured by dexamethasone-induced mitogen-induced protein kinase phosphatase-1 expression in

mononuclear cells isolated from obese asthma patients over a range of BMIs. This suggests that factors specific to the obese state, which include many effects on innate and adaptive immunity, may alter the response to asthma medications.

This altered response to medications needs to be considered in the design of future asthma clinical studies, inasmuch as obesity may be an important covariate that could significantly alter the response to medications. With the increasing prevalence of obesity (world-wide), this will be an important consideration in future asthma studies.

Effect of weight loss in obese asthma patients. A number of studies have reported the effects of weight loss on asthma by surgical or dietary interventions. The majority of the studies of surgical intervention have not measured outcomes specific to asthma but have consistently described decreased medication use and improved symptoms with massive weight loss (13). Maniscalco et al. (45), who used validated asthma questionnaires and performed lung function measurements, reported improved asthma control and spirometric function with weight loss in a cohort of women undergoing bariatric surgery. We are aware of only one randomized controlled trial of dietary intervention for weight loss: Stenius-Aarniala et al. (64) found improved asthma symptoms and peak flow in patients with weight loss. The mechanisms by which weight loss improves asthma control and lung function are not known. Certainly, mechanical factors are likely to be important, but reversal of systemic inflammation and oxidative stress may be equally important: Johnson et al. (28) found reduced levels of markers of oxidative stress with caloric restriction in patients with asthma. Oxidative stress may be important in obese individuals (36).

The effects of weight loss on airway hyperreactivity are not clear. One study reported no significant improvement in airway hyperreactivity with dietary-induced weight loss (1), although whether a more significant weight loss through surgical intervention may improve airway hyperreactivity or airway hyperreactivity would improve in certain subgroups is not known.

The studies of weight loss suggest that asthma control is improved with weight loss and that spirometric lung function and peak flow are improved. This may be associated with reduced levels of oxidative stress. The effects of weight loss on the pathophysiology of disease in the airway are not known.

CHARACTERISTICS OF AIRWAY INFLAMMATION IN OBESE ASTHMA PATIENTS

Classically, asthma is characterized by Th type 2 (Th2)-mediated allergic inflammation; therefore, the presence of atopy as a risk factor for asthma is well recognized. A number of epidemiological studies have investigated the relationship between atopy and obesity to determine whether obesity is a risk factor for allergic responses. In parallel, a number of cross-sectional cohort studies have investigated the relationship between airway eosinophilic inflammation (as a marker of Th2 inflammation) and BMI. Together, these studies address whether obesity is a risk factor for allergic inflammation in general, and airway inflammation, in particular.

Epidemiological studies suggest that obesity is not a risk factor for atopy. Some have reported that the risk of asthma in obesity is not related to atopic status (43), and von Mutius et al. (74) reported no independent relationship between BMI and atopy or eosinophilia in children. Other epidemiological stud-

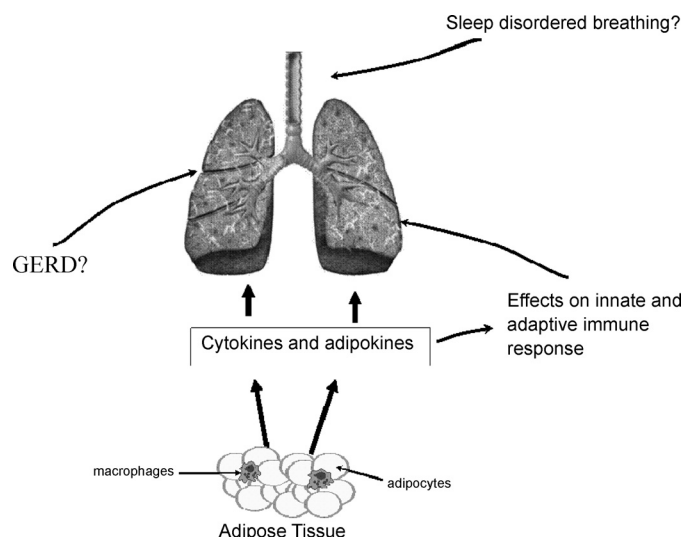


Fig. 1. Adipose tissue can produce mediators that may have direct effects on the lung and also affect the innate and adaptive immune system, which may lead to airway disease. Obesity also increases the risk of other comorbidities, such as sleep disordered breathing and gastroesophageal reflux disease (GERD), which may in turn exacerbate respiratory symptoms and disease.

ies have demonstrated that the OR, or relative risk, of developing asthma is higher in nonallergic than in allergic adults (9, 27, 37) and children (73). On balance, these data suggest that obesity is neither a risk factor for atopy nor a risk factor for allergic asthma.

The characteristics of airway inflammation in obesity have been studied noninvasively in cross-sectional studies using exhaled nitric oxide, induced sputum, and exhaled breath condensate. Exhaled nitric oxide parallels the presence of airway eosinophils (60) and is used in clinical practice as a marker of inflammation and response to therapeutic intervention. Several studies found no significant differences in exhaled nitric oxide measurements between obese and lean asthma patients (31, 41, 48). Studies of induced sputum showed either no relationship between airway cellular inflammation and BMI or an inverse relationship between cellular indexes and BMI: Todd et al. (71) found no relationship between BMI and airway cell counts in asthma patients or nonasthmatic subjects; Sutherland et al. (69) reported similar cell counts in obese and nonobese asthma patients; van Veen et al. (72) found an inverse relationship between sputum eosinophilia and BMI in adult asthma patients; and Lessard et al. (40) found an inverse correlation between waist circumference and airway eosino-

Table 2. *Characteristics of the obese asthma phenotype*

Characteristic	Reference No.
Worse asthma control	50, 70, 76
Decreased response to controller medication	5, 12, 56, 59, 67
Presence of comorbidities related to obesity	11, 19, 39, 42, 66
Presence of metabolic/immune derangements related to obesity	15, 57

philia, with a trend toward an inverse relationship between airway eosinophilia and BMI. Clearly, these studies do not suggest that obesity is associated with increased airway eosinophilic inflammation; in fact, the reverse may be true.

Although obesity is not associated with increased airway eosinophilic inflammation, it may be associated with increased levels of airway oxidative stress. Komakula et al. (36) demonstrated that increased BMI is correlated with increased levels of 8-isoprostane. The significance of increased levels of oxidative stress in the airway of obese individuals requires further investigation (16). In nonobese patients, increased levels of oxidative stress have been associated with more severe asthma (51).

These data suggest that allergic inflammation is not the primary etiology of the increased asthma incidence and severity associated with obesity but that factors related to obesity may act on the airway through mechanisms other than allergic inflammation to increase the burden of disease in the obese asthma patient (53, 69).

PATHOGENESIS OF THE OBESITY-ASTHMA PHENOTYPE

Comorbidities in obesity and asthma. Obesity is associated with multiple comorbidities, including hypertension, hypercholesterolemia, diabetes mellitus, obstructive sleep apnea, gastroesophageal reflux disease (GERD), and depression. Obesity may increase the risk of asthma through comorbidities such as sleep disordered breathing (SDB) and GERD, which may lead to airway disease.

Many authors have speculated that GERD could lead to asthma symptoms in the obese population. GERD is increased in proportion to BMI (17), and GERD has been associated with increased airway hyperresponsiveness and wheezing (2, 21), which may result from vagal nerve stimulation by acid reflux into the distal esophagus and/or microaspiration of acid into the bronchi (22, 63). In some studies, treatment of GERD with medications or surgical intervention with Nissen fundoplication led to improved asthma control (23, 33, 34), although a recent study found that this was not the case for patients with

Table 1. *Relationship between serum adipokines and asthma*

Reference No.	Year	Population	Age	n	Finding
18	2004	Turkey, asthma clinic	Children	135	Leptin increased in asthmatics
20	2004	Turkey, pediatric clinic	Children	43	Leptin increased in asthmatics
44	2004	Sweden, birth cohort	Children	138	No relationship between leptin and asthma
62	2006	US, population-based	Adults	5,876	Leptin increased in asthmatics, more in women
35	2008	Korea, university clinic	Children	240	No relationship between adiponectin/leptin and asthma
52	2008	Germany, population-based	Children	462	Leptin associated with asthma in girls Adiponectin not associated with asthma
61	2008	US, population cohort	Adults	2,890	Adiponectin lower in female asthmatics
25	2009	Korea, university clinic	Adults	90	No relationship between adiponectin/leptin and asthma
26	2009	Finland, population cohort	Children and adults	2,620*	No relationship between adiponectin/leptin and asthma

*Number of adults participating in this cohort in 2001; also included were 3,582 children from baseline visit in 1980 and 2,764 participants in 1986.

minimal symptoms of GERD (even if they were obese individuals in whom GERD was demonstrated by a positive pH probe) (47). The potential contributions of GERD to asthma in an obese individual require further study, but there are few convincing studies to suggest that GERD is a significant contributor to the pathogenesis of asthma in the obese individual.

The prevalence of sleep apnea appears to be increased in severely compared with moderately asthmatic patients of matched BMI (29). This suggests that sleep apnea may be linked to asthma severity, and because obesity is a risk factor for sleep apnea, sleep apnea may be a comorbidity that links poor asthma control and obesity. The mechanisms by which SDB could increase asthma severity are not known, but multiple potential pathways could link asthma and SDB: increased vagal tone, which leads to bronchoconstriction; upper airway inflammation, which leads to lower airway inflammation; and perturbations in central control of bronchomotor tone. Small studies suggest that treatment for sleep apnea improves asthma symptoms but does not affect spirometric lung function or bronchial hyperreactivity (11, 39, 42).

The extent to which SDB and/or GERD contribute to the pathogenesis of asthma in obese individuals is not clear, but they are unlikely to be the whole answer. In a community-based cohort study of ~800 children, Sulit et al. (66) reported that the association between obesity and asthma was strong, even after adjustment for SDB, and Gunnbjornsdottir et al. (19), in a report from the European Community Respiratory Health Survey, stated that obesity remained significantly related to the onset of asthma, even when they controlled for nocturnal GERD and symptoms of SDB. This suggests that although GERD and SDB may contribute to the pathogenesis of asthma in obese individuals, other factors need to be considered (Fig. 1).

Adipokines, obesity, and airway inflammation. One additional link between obesity and asthma may be the adipokines and their effects on airway inflammation. Adipose tissue is a metabolically active tissue participating in energy homeostasis and immune responses (15, 57). Studies of obesity demonstrate that adipose tissue secretes biologically active cytokines, including TNF- α , IL-6, and adipokines, including leptin, adiponectin, and resistin (49). In humans, obesity results in systemic inflammation, characterized by elevated serum levels of these proinflammatory adipokines, chemokines, and acute-phase proteins (65).

Studies in mouse models of obesity and asthma suggest that the adipokines leptin and adiponectin may modulate airway inflammation and bronchial hyperreactivity. Leptin, which is increased in proportion to BMI, has a number of proinflammatory effects on cells involved in innate and adaptive immunity. Adiponectin is a 30-kDa protein with an NH₂-terminal collagenase domain followed by a COOH-terminal globular domain. It exists in low- and high-molecular-weight forms (55). Adiponectin's primary effects are on energy metabolism and are antidiabetic in nature. It also has many anti-inflammatory effects and inhibits production of the proinflammatory cytokines IL-6 and TNF- α (46) while inducing the anti-inflammatory cytokines IL-1 receptor antagonist and IL-10 (38, 77, 78). Serum adiponectin and IL-10 levels are lower in obesity (24) and increase with weight loss (14, 30, 32).

Multiple studies have investigated the relationship between serum levels of these adipokines and the presence of asthma (Table 1). Although the data are sometimes conflicting, there does not appear to be a strong relationship between serum levels of leptin/adiponectin and the presence of asthma sufficient to explain the relationship between asthma and obesity (61, 62). However, serum levels may not accurately reflect levels in the lung, and, in the case of adiponectin in particular, total levels in the serum may not reflect levels of the biologically active multimer of adiponectin. It may also be that local expression of these adipokines needs to be considered: Bruno et al. (6) showed that bronchial epithelium expresses leptin and leptin receptor and that expression of leptin and leptin receptor is altered in severe asthma. This suggests not only that leptin may have a role in the pathogenesis of asthma (in obese and normal-weight individuals), a finding that needs further investigation, but that serum levels may not reflect biologically active levels in the compartment of interest, in this case, the airway.

SUMMARY

Asthma is associated with airway inflammation and reversible airflow obstruction. Obese asthma patients have more severe disease with increased asthma exacerbations, decreased asthma control, and decreased steroid responsiveness. Obese asthma patients do not demonstrate increased cellular airway inflammation, possibly because of the presence of a non-Th2 cytokine-driven, nonallergic asthma phenotype. This phenotype may result, because comorbidities such as GERD and SDB may contribute to the presentation of asthma in the obese. There is also increasing evidence that cytokines secreted by adipose tissue cause systemic inflammation that may affect the lung (Fig. 1). Weight loss is associated with improvement in lung function, medication use, symptoms, morbidity, and health status. Obesity likely results in a unique asthma phenotype (Table 2) that will require the development of a distinct therapeutic approach.

GRANTS

N. L. Lugogo is supported by National Heart, Lung, and Blood Institute Grants P50-HL-084917 and R01-HL-064619 and the American Thoracic Society. M. Kraft is supported by National Institutes of Health Grants R01-HL-064619, R01-HL-086887, P50-HL-084917, and U01-AI-066590. A. E. Dixon is supported by National Institutes of Health Grants P20-RR-15557 and K23-RR-019965 and the American Lung Association.

DISCLOSURES

M. Kraft receives research funding from GlaxoSmithKline, Asthmatx, Biomarck, GE Healthcare, Bronchus, Novartis, and Genentech and has served as a speaker and advisor for GlaxoSmithKline in the past 12 months.

REFERENCES

1. 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* 125: 2046–2052, 2004.
2. Bagnato GF, Gulli S, Giacobbe O, De Pasquale R, Purrello D'Ambrosio F. Bronchial hyperresponsiveness in subjects with gastroesophageal reflux. *Respiration* 67: 507–509, 2000.
3. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 175: 661–666, 2007.
4. Bibi H, Shoseyov D, Feigenbaum D, Genis M, Friger M, Peled R, Sharff S. The relationship between asthma and obesity in children: is it real or a case of over diagnosis? *J Asthma* 41: 403–410, 2004.

5. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med* 101: 2240–2247, 2007.
6. Bruno A, Pace E, Chanez P, Gras D, Vachier I, Chiappara G, La Guardia M, Gerbino S, Profita M, Gjomarkaj M. Leptin and leptin receptor expression in asthma. *J Allergy Clin Immunol* 124: 230–237, 2009.
7. 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* 159: 2582–2588, 1999.
8. Centers for Disease Control. *Overweight and Obesity* (Online). Centers for Disease Control. <http://www.cdc.gov/obesity/data/trends.html> [25 Sep 2009].
9. Chen Y, Dales R, Jiang Y. The association between obesity and asthma is stronger in nonallergic than allergic adults. *Chest* 130: 890–895, 2006.
10. Chen Y, Dales R, Tang M, Krewski D. Obesity may increase the incidence of asthma in women but not in men: longitudinal observations from the Canadian National Population Health Surveys. *Am J Epidemiol* 155: 191–197, 2002.
11. Ciftci TU, Ciftci B, Guven SF, Kokturk O, Turktaş H. Effect of nasal continuous positive airway pressure in uncontrolled nocturnal asthmatic patients with obstructive sleep apnea syndrome. *Respir Med* 99: 529–534, 2005.
12. 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* 43: 553–558, 2006.
13. Eneli IU, Skybo T, Camargo CA Jr. Weight loss and asthma: a systematic review. *Thorax* 63: 671–676, 2008.
14. Engeli S, Feldpausch M, Gorzelski 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* 52: 942–947, 2003.
15. Ferrante AW Jr. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. *J Inter Med* 262: 408–414, 2007.
16. Friedenberg FK, Xanthopoulos M, Foster GD, Richter JE. The association between gastroesophageal reflux disease and obesity. *Am J Gastroenterol* 103: 2111–2122, 2008.
17. Guler N, Kircirler E, Ones U, Tamay Z, Salmayenli N, Darendeliler F. Leptin: does it have any role in childhood asthma? *J Allergy Clin Immunol* 114: 254–259, 2004.
18. 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, Svane C, Toren K, Tunsater A, Lillienberg L, Gislason D, Blondal T, Bjornsdottir US, Jorundsdottir KB, Talvik R, Forsberg B, 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* 24: 116–121, 2004.
19. Gurkan F, Atamer Y, Ece A, Kocyigit Y, Tuzun H, Mete N. Serum leptin levels in asthmatic children treated with an inhaled corticosteroid. *Ann Allergy Asthma Immunol* 93: 277–280, 2004.
20. Hancox RJ, Poulton R, Taylor DR, Greene JM, McLachlan CR, Cowan JO, Flannery EM, Herbison GP, Sears MR, Talley NJ. Associations between respiratory symptoms, lung function and gastro-oesophageal reflux symptoms in a population-based birth cohort. *Respir Res* 7: 142, 2006.
21. Harding SM. Gastroesophageal reflux, asthma, and mechanisms of interaction. *Am J Med* 111 Suppl 8A: 8S–12S, 2001.
22. Harding SM. Gastroesophageal reflux: a potential asthma trigger. *Immunol Allergy Clin North Am* 25: 131–148, 2005.
23. Hotta K, Funahashi T, Bodkin NL, Ortmeier HK, Arita Y, Hansen BC, Matsuzawa Y. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. *Diabetes* 50: 1126–1133, 2001.
24. Jang AS, Kim TH, Park JS, Kim KU, Uh ST, Seo KH, Kim YH, Lim GI, Park CS. Association of serum leptin and adiponectin with obesity in asthmatics. *J Asthma* 46: 59–63, 2009.
25. Jartti T, Saarikoski L, Jartti L, Lisinen I, Jula A, Huupponen R, Viikari J, Raitakari OT. Obesity, adipokines and asthma. *Allergy* 64: 770–777, 2009.
26. 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* 32: 831–837, 2002.
27. Johnson JB, Summer W, Cutler RG, Martin B, Hyun DH, Dixit VD, Pearson M, Nassar M, Telljohann R, Maudsley S, Carlson O, John S, Laub DR, Mattson MP. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radic Biol Med* 42: 665–674, 2007.
28. 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* 124: 371–376, 2009.
29. Jung SH, Park HS, Kim KS, Choi WH, Ahn CW, Kim BT, Kim SM, Lee SY, Ahn SM, Kim YK, Kim HJ, Kim DJ, Lee KW. Effect of weight loss on some serum cytokines in human obesity: increase in IL-10 after weight loss. *J Nutr Biochem* 19: 371–375, 2008.
30. 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* 116: 929–930, 2005.
31. Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor- α expression. *Diabetes* 52: 1779–1785, 2003.
32. Kiljander T, Salomaa ER, Hietanen E, Helenius H, Liippo K, Terho EO. Asthma and gastro-oesophageal reflux: can the response to anti-reflux therapy be predicted? *Respir Med* 95: 387–392, 2001.
33. Kiljander TO, Salomaa ER, Hietanen EK, Ovaska J, Helenius H, Liippo K. Gastroesophageal reflux and bronchial responsiveness: correlation and the effect of fundoplication. *Respiration* 69: 434–439, 2002.
34. Kim KW, Shin YH, Lee KE, Kim ES, Sohn MH, Kim KE. Relationship between adipokines and manifestations of childhood asthma. *Pediatr Allergy Immunol* 19: 535–540, 2008.
35. Komakula S, Khatri S, Mermis J, Savill S, Haque S, Rojas M, Brown L, Teague GW, Holguin F. Body mass index is associated with reduced exhaled nitric oxide and higher exhaled 8-isoprostanes in asthmatics. *Respir Res* 8: 32, 2007.
36. Kronander UN, Falkenberg M, Zetterstrom O. Prevalence and incidence of asthma related to waist circumference and BMI in a Swedish community sample. *Respir Med* 98: 1108–1116, 2004.
37. Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K, Maeda K, Nagaretani H, Kishida K, Maeda N, Nagasawa A, Funahashi T, Matsuzawa Y. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. *Circulation* 109: 2046–2049, 2004.
38. Lafond C, Series F, Lemiere C. Impact of CPAP on asthmatic patients with obstructive sleep apnoea. *Eur Respir J* 29: 307–311, 2007.
39. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? *Chest* 134: 317–323, 2008.
40. Leung TF, Li CY, Lam CW, Au CS, Yung E, Chan IH, Wong GW, Fok TF. The relation between obesity and asthmatic airway inflammation. *Pediatr Allergy Immunol* 15: 344–350, 2004.
41. Lin CC, Lin CY. Obstructive sleep apnea syndrome and bronchial hyperreactivity. *Lung* 173: 117–126, 1995.
42. Loerbroeks A, Apfelbacher CJ, Amelang M, Sturmer T. Obesity and adult asthma: potential effect modification by gender, but not by hay fever. *Ann Epidemiol* 18: 283–289, 2008.
43. Mai XM, Bottcher MF, Leijon I. Leptin and asthma in overweight children at 12 years of age. *Pediatr Allergy Immunol* 15: 523–530, 2004.
44. 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* 102: 102–108, 2008.
45. Masaki T, Chiba S, Tatsukawa H, Yasuda T, Noguchi H, Seike M, Yoshimatsu H. Adiponectin protects LPS-induced liver injury through modulation of TNF- α in KK-Ay obese mice. *Hepatology* 40: 177–184, 2004.
46. Mastroratte JG, Anthonisen NR, Castro M, Holbrook JT, Leone FT, Teague WG, Wise RA. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med* 360: 1487–1499, 2009.
47. McLachlan CR, Poulton R, Car G, Cowan J, Filsell S, Greene JM, Taylor DR, Welch D, Williamson A, Sears MR, Hancox RJ. Adiposity, asthma, and airway inflammation. *J Allergy Clin Immunol* 119: 634–639, 2007.

49. Milan G, Granzotto M, Scarda A, Calcagno A, Pagano C, Federspil G, Vettor R. Resistin and adiponectin expression in visceral fat of obese rats: effect of weight loss. *Obes Res* 10: 1095–1103, 2002.
50. Mosen DM, Schatz M, Magid DJ, Camargo CA Jr. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol* 122: 507–511, 2008.
51. Nadeem A, Masood A, Siddiqui N. Oxidant-antioxidant imbalance in asthma: scientific evidence, epidemiological data and possible therapeutic options. *Ther Adv Respir Dis* 2: 215–235, 2008.
52. Nagel G, Koenig W, Rapp K, Wabitsch M, Zoellner I, Weiland SK. Associations of adipokines with asthma, rhinoconjunctivitis, and eczema in German schoolchildren. *Pediatr Allergy Immunol* 20: 81–88, 2009.
53. Nicolacakis K, Skowronski ME, Coreno AJ, West E, Nader NZ, Smith RL, McFadden ER Jr. Observations on the physiological interactions between obesity and asthma. *J Appl Physiol* 105: 1533–1541, 2008.
54. Nystad W, Meyer HE, Nafstad P, Tverdal A, Engeland A. Body mass index in relation to adult asthma among 135,000 Norwegian men and women. *Am J Epidemiol* 160: 969–976, 2004.
55. Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, Wagner JA, Wu M, Knopps A, Xiang AH, Utzschneider KM, Kahn SE, Olefsky JM, Buchanan TA, Scherer PE. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. *J Biol Chem* 279: 12152–12162, 2004.
56. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. *Eur Respir J* 27: 495–503, 2006.
57. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. *J Clin Endocrinol Metab* 93: S64–S73, 2008.
58. Rizwan S, Reid J, Kelly Y, Bundred PE, Pearson M, Brabin BJ. Trends in childhood and parental asthma prevalence in Merseyside, 1991–1998. *J Public Health* 26: 337–342, 2004.
59. Rodrigo GJ, Plaza V. Body mass index and response to emergency department treatment in adults with severe asthma exacerbations: a prospective cohort study. *Chest* 132: 1513–1519, 2007.
60. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, Taylor DR. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med* 169: 473–478, 2004.
61. 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* 63: 877–882, 2008.
62. Sood A, Ford ES, Camargo CA Jr. Association between leptin and asthma in adults. *Thorax* 61: 300–305, 2006.
63. Stein MR. Possible mechanisms of influence of esophageal acid on airway hyperresponsiveness. *Am J Med* 115 Suppl 3A: 55S–59S, 2003.
64. 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* 320: 827–832, 2000.
65. Straczkowski M, Dzienis-Straczowska S, Stepień A, Kowalska I, Szelachowska M, Kinalska I. Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor- α system. *J Clin Endocrinol Metab* 87: 4602–4606, 2002.
66. Sulit LG, Storfer-Isser A, Rosen CL, Kirchner HL, Redline S. Associations of obesity, sleep-disordered breathing, and wheezing in children. *Am J Respir Crit Care Med* 171: 659–664, 2005.
67. Sutherland ER, Goleva E, Strand M, Beutner DA, Leung DY. Body mass and glucocorticoid response in asthma. *Am J Respir Crit Care Med* 178: 682–687, 2008.
68. 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* 123: 1328–1334, 2009.
69. 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* 178: 469–475, 2008.
70. 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* 63: 14–20, 2008.
71. 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* 37: 1049–1054, 2007.
72. 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* 63: 570–574, 2008.
73. von Kries R, Hermann M, Grunert VP, von Mutius E. Is obesity a risk factor for childhood asthma? *Allergy* 56: 318–322, 2001.
74. von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax* 56: 835–838, 2001.
75. Vortmann M, Eisner MD. BMI and health status among adults with asthma. *Obesity (Silver Spring)* 16: 146–152, 2008.
76. Wen XJ, Balluz L, Mokdad A. Do obese adults have a higher risk of asthma attack when exposed to indoor mold? A study based on the 2005 Behavioral Risk Factor Surveillance System. *Public Health Rep* 124: 436–441, 2009.
77. Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. *Biochem Biophys Res Commun* 323: 630–635, 2004.
78. Wulster-Radcliffe MC, Ajuwon KM, Wang J, Christian JA, Spurlock ME. Adiponectin differentially regulates cytokines in porcine macrophages. *Biochem Biophys Res Commun* 316: 924–929, 2004.