

Relationship between adipokines and manifestations of childhood asthma

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Although the prevalences of asthma and obesity are increasing substantially in recent decades, very little is known about the possible association between them. We evaluated the roles of leptin, adiponectin, and resistin, which are adipokines produced by adipose tissue, on childhood asthma, and their association with pulmonary function and bronchial hyperresponsiveness. We studied 149 atopic asthmatic children, 37 non-atopic asthmatic children, and 54 healthy children. Body mass index was calculated using height and weight, which were measured on the same day that pulmonary function tests and methacholine challenge tests were performed. Skin prick tests were performed, and total eosinophil count, total serum immunoglobulin E (IgE), serum eosinophil cationic protein, leptin, adiponectin, and resistin were measured in all subjects. Atopic asthmatics had lower resistin levels compared with non-atopic asthma and control groups, but leptin and adiponectin did not show any difference among these three groups. Resistin demonstrated positive correlation with methacholine PC₂₀ and negative correlations with eosinophil count and serum total IgE. Leptin and adiponectin showed associations with forced expiratory volume in 1 s or forced expiratory flow between 25–75%. Multiple regression analysis revealed that resistin was a significant predictive factor for asthma. There was no direct association between asthma and leptin or adiponectin. Our findings suggest that resistin may play a negative predictive role in asthma. Adiponectin and leptin showed close associations with pulmonary function and may have disease-modifying effects in children with asthma.

Kyung W. Kim¹, Youn H. Shin², Kyung E. Lee¹, Eun S. Kim¹, Myung H. Sohn¹ and Kyu-Earn Kim¹

¹Department of Pediatrics and Institute of Allergy, Brain Korea 21 Project for Medical Sciences, Research Center for Human Natural Defense System, Yonsei University College of Medicine, Seoul, Korea, ²Department of Pediatrics, Pochon CHA University College of Medicine, Seoul, Korea

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Myung Hyun Sohn, Department of Pediatrics and Institute of Allergy, Yonsei University College of Medicine, Severance Hospital, CPO Box 8044, Seoul 120-752, Korea
Tel.: +82 2 2228 2062
Fax: +82 2 393 9118
E-mail: mhsohn@yumc.yonsei.ac.kr

Kyung Won Kim and Youn Ho Shin contributed equally to this work. This study was supported by Bumsuk Academy Research Fund by 2005.

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The prevalences of asthma and obesity have increased substantially during the last several decades in many countries, leading to the speculation that obese people might be at increased risk of asthma (1, 2). Although a large number of studies such as cross-sectional, case-control, prospective, and weight loss studies have been performed, the possibility that obesity might increase the risk of asthma development remains controversial (3). Nevertheless, potential mechanisms have been suggested including obesity-related changes in lung volumes, systemic inflammation, and adipocyte-derived factors, such as the pro-inflammatory and anti-inflam-

matory factors, which include leptin, adiponectin, and resistin (4, 5).

Leptin is a 16-kDa protein encoded by the *ob* gene that plays a key role in the regulation of body weight (6). Leptin may provide a link between inflammation and T-cell function in patients with asthma, as well as regulate appetite and energy balance of the body (4, 6, 7). For example, recent studies have shown that higher leptin levels are a predictive factor for asthma in children, independent of body mass index (BMI) (7). Adiponectin, also known as adipocyte complement-related protein of 30 kDa (ACRP30), adipoQ, and gelatin-binding protein of 28 kDa

(GBP28), is an adipocyte-specific, secreted protein involved in glucose and lipid homeostasis (6). Adiponectin might play a role as an anti-inflammatory hormone that inhibits the production of tumor necrosis factor (TNF)- α , Interleukin-6 (IL-6), and nuclear factor κ B (NF- κ B), inducing IL-10 and IL-1 receptor antagonists as well (4). Human resistin, a 12.5-kDa protein, contains 108 amino acids as a pre-peptide, and belongs to the family of resistin-like molecules (RELMs), also known as 'found in inflammatory zone' (FIZZ) (4, 6). Very little is known about the potential function of resistin (FIZZ-3) although it has been suggested to have adhesion molecule-upregulating effects (4).

The aim of this study was to evaluate the roles of leptin, adiponectin, and resistin in childhood asthma and their effect on the levels of atopy markers, pulmonary function, and bronchial hyperresponsiveness.

Materials and methods

Subjects

Two hundred forty subjects were recruited from Severance Children's Hospital, Yonsei University College of Medicine, together comprising 121 boys and 119 girls (mean age, 9.8 ± 2.1 yr), regardless of the state of obesity. Current asthma was defined as recurrent wheezing or coughing episodes in the absence of a cold in the preceding 12 months, with a physician's diagnosis of bronchial hyperresponsiveness upon methacholine challenge ($PC_{20} \leq 16$ mg/ml) and at least 12% of reversibility of forced expiratory volume in 1 s (FEV_1) after inhalation of β_2 agonist, as per criteria of the American Thoracic Society (ATS) (8). All participants were enrolled before administration of oral or inhaled corticosteroids. Patients treated with systemic corticosteroids because of asthma exacerbation in the preceding 6 months were excluded. Control participants were age-matched healthy children who visited the hospital for general health work-up or vaccination and had no history of wheezing, recurrent or chronic diseases, infection during the preceding two weeks, or hyperresponsiveness to methacholine. Controls also had to be negative for common allergens demonstrated by skin prick test.

For all participants, height and weight were measured in light clothing without shoes to calculate BMI in kilogram per square meter. Obesity and overweight were defined by BMI for age and sex based on an international survey (9). Absolute BMI values were then converted to

previously established BMI percentiles of Korean children for data analysis (10).

Informed written consent was obtained from all participants before inclusion in the study, approved by the Severance Hospital Institutional Review Board beforehand.

Spirometry and methacholine challenge test

Lung function was measured by spirometry (Vmax encore; VIASYS Healthcare Inc., Conshohocken, PA, USA) and evaluated according to the ATS standards. Bronchial hyperresponsiveness was assessed in all participants through performing methacholine challenge test. Children were eligible if they could perform reproducible spirometry and had an FEV_1 of at least 70% of the predicted value (11). In short, after saline inhalation, doses of methacholine (0.075, 0.15, 0.31, 0.62, 1.25, 2.5, 5, 10, and 25 mg/ml) were delivered for 0.6 s through a DeVilbiss 646 nebulizer using a Rosenthal-French dosimeter (Ferraris, Hertford, England) until either FEV_1 decreased by 20% or more, or the highest dose was administered. FEV_1 was measured within 60–90 s after each inhalation. The concentration of methacholine inducing a 20% decrease in FEV_1 (PC_{20}) was determined, and the challenge test was considered positive if the PC_{20} was 16 mg/ml or less. Anti-inflammatory preparations and bronchodilators were withheld for 24 h before the test.

Skin prick tests

Skin prick tests were performed by using a panel of common allergens including house dust mite, mold mix, tree mix, grass mix, weed mix, cat, dog, cockroach, cow's milk, and egg (Torii & Co., Tokyo, Japan), together with negative (saline) and positive (histamine HCl) controls. Wheal sizes were measured 15 min after pricking. A positive reaction was defined as a wheal with a diameter exceeding the negative control by at least 3 mm. Children were considered to be atopic if they had at least one positive skin prick test response or an immunoglobulin E (IgE) level over 100 IU/ml.

Measurement of blood eosinophils, serum total IgE, eosinophil cationic protein (ECP), leptin, adiponectin, and resistin

The NE-8000 system (Sysmex, Kobe, Japan) was used to count eosinophils automatically in peripheral blood, whereas serum total IgE and ECP were measured with CAP radioallergosorbent technique (UniCAP; Pharmacia and

Upjohn, Uppsala, Sweden). Blood samples to check serum adipokine levels were obtained between 6 AM and 9 AM after an overnight fast. After clotting at 4°C, the serum was separated by centrifugation at 1300 *g* for 10 min and stored at -70°C until the assays were performed. Serum leptin, adiponectin, and resistin were measured individually with ELISA kits (R&D Systems, Inc., Minneapolis, MN, USA) according to the manufacturer's instructions. The minimum detection limits of leptin, adiponectin, and resistin were 0.78 ng/ml, 0.20 µg/ml, and 0.16 ng/ml, respectively. All assays were performed in duplicate for each sample, with the mean values reported here.

Statistical analysis

Numerical variables were reported as mean ± s.d. Numerical parameters with non-normal distribution (age, BMI percentile, eosinophil count, serum total IgE, ECP, leptin, and resistin levels) were reported as medians and interquartile range and were log transformed before analysis. Comparisons among groups divided by BMI percentile and by diagnosis were evaluated by using one-way ANOVA, Kruskal-Wallis, or chi-square tests. Correlations between serum adipokine levels and lung function, bronchial hyperresponsiveness, or markers of atopy were calculated with Pearson's correlation test. Multiple logistic regression model was used for estimating the association between adipokines and the dependent variable, asthma. This multivariate analysis was adjusted for age, sex, BMI percentile, and adipokines mutually. *p*-Values < 0.05 were considered statistically significant. The SPSS software (version 13.0, SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

The study participants included 149 patients with atopic asthma, 37 patients with non-atopic asthma, and 54 controls. Resistin levels differed significantly among atopic asthma, non-atopic asthma, and control groups. However, adiponectin and leptin levels, as well as BMI percentile, did not differ among the three groups. There was a statistically significant difference in eosinophil count, serum total IgE, ECP, FEV₁, and FEF25–75% among these groups (Table 1).

Correlation results between adipokines and lung function or bronchial hyperresponsiveness are shown in Table 2. Serum leptin levels demonstrated negative correlations with baseline FEV₁ and FEF25–75%. Serum adiponectin levels showed significant positive correlation with FEF25–75%. However, serum resistin levels showed significant positive correlation with methacholine PC₂₀.

Correlation coefficients between adipokines and markers of atopy are shown in Table 3. Serum resistin levels demonstrated negative correlations with eosinophil count and serum total IgE, but leptin and adiponectin did not show any correlation with markers of atopy.

Multiple regression analysis was performed with asthma as the dependent variable, and age, sex, BMI percentile, log leptin, adiponectin, and log resistin as independent variables (Table 4). Results that indicated low log resistin contributed significantly to asthma.

Adipokine levels differed significantly among the normoweight (*n* = 158, 66%), overweight (*n* = 43, 18%), and obesity (*n* = 39, 16%) groups (leptin, *p* < 0.001; adiponectin, *p* < 0.001; resistin, *p* = 0.044, respectively). However, there was no difference in other vari-

Table 1. Anthropometric, lung function and atopy parameters and adipokines of children classified by diagnosis

	Atopic asthma	Non-atopic asthma	Control	<i>p</i>
No. of participants	149	37	54	
Female/male	51/98	12/25	26/28	0.157
Age (years)	10.1 (8.8–11.5)	9.0 (8.2–10.9)	9.1 (8.0–11.1)	0.413
BMI percentile	75.0 (42.3–90.0)	76.0 (56.0–91.5)	68.5 (35.0–93.0)	0.447
Normoweight/risk of overweight/obesity (%)	101/26/22 (67.8/17.4/14.8)	23/8/6 (62.2/21.6/16.2)	34/9/11 (63/16.7/20.4)	0.854
FVC (% predicted)	85.06 ± 12.14	88.44 ± 16.09	90.02 ± 10.23	0.115
Baseline FEV ₁ (% predicted)	79.90 ± 12.52	86.91 ± 17.09	90.89 ± 10.31	0.003
FEF25–75% (% predicted)	76.52 ± 22.38	88.70 ± 21.32	91.72 ± 21.79	<0.001
Eosinophil count (/µl)	495 (270–775)	210 (145–275)	160 (80–215)	<0.001
Serum total IgE (U/ml)	342.0 (140.5–940.5)	46.0 (16.0–91.0)	38.5 (26.9–92.3)	<0.001
Serum ECP (µg/l)	16.0 (7.8–37.3)	9.5 (4.3–17.8)	7.1 (3.6–11.2)	<0.001
Leptin (ng/ml)	2.27 (0.65–5.03)	2.22 (0.96–3.29)	2.10 (0.71–4.49)	0.607
Adiponectin (µg/ml)	7.60 ± 3.84	8.10 ± 4.73	7.32 ± 4.19	0.670
Resistin (ng/ml)	11.98 (8.31–16.92)	13.49 (6.54–31.40)	15.65 (9.82–28.21)	0.015

Data are presented as absolute numbers, mean ± s.d., or median (interquartile range).

Table 2. Correlation coefficients between adipokines, and lung function or bronchial hyperresponsiveness

	FVC (% predicted)	Baseline FEV ₁ (% predicted)	FEF25–75% (% predicted)	PC ₂₀ (log mg/ml)
Leptin (log ng/ml)				
r	–0.086	–0.216	–0.172	0.007
p	0.224	0.002	0.014	0.911
Adiponectin (μg/ml)				
r	–0.048	0.073	0.193	–0.041
p	0.493	0.300	0.006	0.529
Resistin (log ng/ml)				
r	0.093	0.111	0.076	0.162
p	0.190	0.116	0.286	0.013

Table 3. Correlation coefficients between adipokines and markers of atopy

	Eosinophil count (log/μl)	Serum total IgE (log IU/ml)	Serum ECP (log μg/l)
Leptin (log ng/ml)			
r	0.086	0.036	0.014
p	0.212	0.596	0.850
Adiponectin (μg/ml)			
r	–0.001	–0.015	0.028
p	0.993	0.816	0.687
Resistin (log ng/ml)			
r	–0.153	–0.154	0.035
p	0.019	0.018	0.619

Table 4. Prediction analysis for asthma

	Odds ratio	95% CI	p-value
Sex	0.592	0.293–1.196	0.144
Age	1.107	0.926–1.323	0.263
BMI percentile	1.008	0.993–1.024	0.301
Log leptin	0.940	0.652–1.354	0.738
Adiponectin	1.058	0.968–1.156	0.216
Log resistin	0.587	0.352–0.981	0.042

Analysis are adjusted for age, sex, BMI percentile, and adipokines.

ables, such as blood eosinophil count, serum total IgE, ECP levels, forced vital capacity (FVC), FEV₁, FEF25–75%, and PC₂₀, among these groups (data not shown). Serum leptin ($\gamma = 0.537$, $p < 0.001$) and adiponectin ($\gamma = -0.239$, $p < 0.001$) demonstrated correlations with BMI percentile while serum resistin did not.

Discussion

Resistin has been shown to affect the susceptibility to asthma, as well as to correlate with eosinophil count, serum total IgE, and methacholine PC₂₀. Analysis of leptin and adiponectin indicated that they are associated with some pulmonary function parameters, FEV₁ or FEF25–75%.

Recently, resistin, a new adipocyte hormone, and its functional importance in diabetes have been discovered (12). It would work as an important link between increased fat mass and insulin resistance. Additional actions of resistin remain unclear, and several inconsistencies have emerged. Recent data indicate that stimulation of macrophages *in vitro* with endotoxin and pro-inflammatory cytokines leads to a marked increase in resistin production (13). A few reports have investigated the effects of resistin in the modulation of inflammatory responses, showing that resistin upregulates the expression of monocyte chemo-attractant protein (MCP)-1, as well as vascular cell adhesion molecule 1 and intercellular adhesion molecule (ICAM)-1, in endothelial cells, which have been known to related with allergic inflammation (14). In this study, atopic asthmatics had the lowest serum resistin levels. Resistin was negatively associated with eosinophil count and log serum IgE, and positively associated with methacholine PC₂₀ in correlation analyses. Furthermore, resistin was shown to be a negative predictive factor for the occurrence of asthma. These results have implied that resistin may take a part in the pathogenesis of asthma. Several evidences support our results that resistin may regulate certain inflammatory responses such as adhesion molecule-upregulating effects (14). However, it has not been reported whether resistin plays a role in the pathophysiology of asthma yet. Our results indicate that resistin may affect asthma more than leptin, which was reported to play a role in asthma pathogenesis (7).

Leptin has been implicated in the pathogenesis of asthma in obesity in recent years (7, 15–17). In animal models, it has been found that changes in methacholine responsiveness and IgE are augmented in leptin-infused mice (16). Clinical studies provide supporting evidence to the mouse-model observation that leptin may play a role in asthma that is to some extent independent of obesity (7, 15, 17). However, the mechanisms still remain unknown, and the relationship between asthma and leptin is inconsistent when regarding sex (7, 17). Our results found that serum leptin levels did not differ among atopic asthma, non-atopic asthma, and control groups, but leptin showed correlations to FEV₁ and FEF25–75%. These show the close association between leptin and pulmonary function even if there is no direct association between leptin and asthma. The association might be responsible for the effects of leptin on inflammation and lung development. Leptin, which exerts pro-inflammatory effect, might alter the Th1/Th2

balance in obese subjects through Th1 cell differentiation and cytokine production, such as TNF- α , transforming growth factor (TGF)- β , IL-1 β , and IL-6 (4, 18). This pro-inflammatory state might modulate airway inflammation which alters lung physiology. In addition, leptin is thought to play a role in the intrauterine, neonatal, and post-natal development of murine lung (19).

Adiponectin is an adipokine that circulates at the highest levels and appears to act as an anti-inflammatory molecule, which induces IL-10 and IL-1 receptor antagonists, and reduces the production of IL-6 and TNF- α -induced NF- κ B signaling (4). In addition, serum adiponectin was reduced during pulmonary allergic reactions, and adiponectin treatment attenuated allergic airway inflammation and airway hyperresponsiveness in mice (20). We found that adiponectin was correlated with FEF25–75%, known as a parameter of small airway function influenced by airway smooth muscle. Additional studies are needed to determine the mechanism on airway smooth muscle.

It has long been recognized that obesity affects lung function. It is likely that obesity evokes a reduction in respiratory system compliance, lung volume, and peripheral airway diameter, as well as alteration in pulmonary blood volume and ventilation-perfusion mismatch (18). However, our findings support that there is no direct association between BMI groups and pulmonary function, bronchial hyperresponsiveness, or asthma itself. There were also no differences in atopy parameters, such as eosinophil count and serum total IgE and ECP, among the normoweight, overweight, and obesity groups in our study. Results of the present study correspond well with those of the earlier study which reported that BMI itself is not associated with either airflow obstruction or airway hyperresponsiveness (21, 22). However, these findings are not in accord with other studies reporting a higher percentage of obese children having bronchial hyperreactivity compared with non-obese children (23). The Childhood Asthma Management Program (CAMP) study suggested that BMI is associated with FEV₁/FVC, not with airway hyperresponsiveness (24). There is more heterogeneity in the epidemiologic studies regarding the association between asthma and obesity (25–27). Recent studies have also not shown a consistent relationship between obesity and atopy (28–30). The possible limitation of our results could be that there were relatively small numbers of participants. Many questions and inconsistencies still remain to be answered yet. Asthma or atopy, and

obesity may share common genetic and environmental causes, which could be mechanical, developmental, hormonal, signal transduction, or immunologic mechanisms. Among these, white adipose tissue is emerging as an active participant in the regulation of pathologic processes, including inflammation. For these reasons, this study was attempted to explore the relations between adipokines and childhood asthma or atopy, in spite of no direct relationship between BMI and asthma or atopy in this study.

In conclusion, our findings suggest that resistin may have a protective effect against asthma. In addition, leptin and adiponectin showed close associations with some pulmonary function parameters and may have disease-modifying effects in children with asthma.

References

- MASOLI M, FABIAN D, HOLT S, BEASLEY R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004; 59: 469–78.
- WORLD HEALTH ORGANIZATION. Obesity: preventing and managing the global epidemic. Geneva (Switzerland): WHO Technical Report Series 894, 2000.
- FORD ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005; 115: 897–909.
- FANTUZZI G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005; 115: 911–9.
- SHORE SA, FREDBERG JJ. Obesity, smooth muscle, and airway hyperresponsiveness. *J Allergy Clin Immunol* 2005; 115: 925–7.
- MEIER U, GRESSNER AM. Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. *Clin Chem* 2004; 50: 1511–25.
- GULER N, KIRERLERI E, ONES U, TAMAY Z, SALMAYENLI N, DARENDELILIR F. Leptin: does it have any role in childhood asthma? *J Allergy Clin Immunol* 2004; 114: 254–9.
- CRAPO RO, CASABURI R, COATES AL, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000; 161: 309–29.
- COLE TJ, BELLIZZI MC, FLEGAL KM, DIETZ WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; 320: 1240–3.
- HONG YM, MOON KR, SEO JW, et al. Nationwide study on body mass index, skinfold thickness, and arm circumference in Korean children. *J Korean Pediatr Soc* 1999; 42: 1186–200.
- YOON KA, LIM HS, KIM H, KOH YY. Normal predicted values of pulmonary function test in Korean school-aged children. *J Korean Pediatr Soc* 1993; 36: 25–37.
- STEPPAN CM, LAZAR MA. The current biology of resistin. *J Intern Med* 2004; 255: 439–47.
- LEHRKE M, REILLY MP, MILLINGTON SC, IQBAL N, RADER DJ, LAZAR MA. An inflammatory cascade leading to hyperresistinemia in humans. *PLoS Med* 2004; 1: e45.

14. KAWANAMI D, MAEMURA K, TAKEDA N, et al. Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: a new insight into adipocytokine-endothelial cell interactions. *Biochem Biophys Res Commun* 2004; 314: 415-9.
15. 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* 2004; 93: 277-80.
16. SHORE SA, SCHWARTZMAN IN, MELLEMA MS, FLYNT L, IMRICH A, JOHNSTON RA. Effect of leptin on allergic airway responses in mice. *J Allergy Clin Immunol* 2005; 115: 103-9.
17. SOOD A, FORD ES, CAMARGO CA JR. Association between leptin and asthma in adults. *Thorax* 2006; 61: 300-5.
18. BEUTHER DA, WEISS ST, SUTHERLAND ER. Obesity and asthma. *Am J Respir Crit Care Med* 2006; 174: 112-9.
19. BERGEN HT, CHERLET TC, MANUEL P, SCOTT JE. Identification of leptin receptors in lung and isolated fetal type II cells. *Am J Respir Cell Mol Biol* 2002; 27: 71-7.
20. SHORE SA, TERRY RD, FLYNT L, XU A, HUG C. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. *J Allergy Clin Immunol* 2006; 118: 389-95.
21. BIBI H, SHOSEYOV D, FEIGENBAUM D, et al. The relationship between asthma and obesity in children: is it real or a case of over diagnosis? *J Asthma* 2004; 41: 403-10.
22. SCHACHTER LM, PEAT JK, SALOME CM. Asthma and atopy in overweight children. *Thorax* 2003; 58: 1031-5.
23. CASTRO-RODRIGUEZ JA, HOLBERG CJ, MORGAN WJ, WRIGHT AL, MARTINEZ FD. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med* 2001; 163: 1344-9.
24. TANTISIRA KG, LITONJUA AA, WEISS ST, FUHLBRIGGE AL. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). *Thorax* 2003; 58: 1036-41.
25. CHINN S, RONA RJ. Can the increase in body mass index explain the rising trend in asthma in children? *Thorax* 2001; 56: 845-50.
26. GOLD DR, DAMOKOSH AI, DOCKERY DW, BERKEY CS. Body-mass index as a predictor of incident asthma in a prospective cohort of children. *Pediatr Pulmonol* 2003; 36: 514-21.
27. TO T, VYDYKHAN TN, DELL S, TASSOUDJI M, HARRIS JK. Is obesity associated with asthma in young children? *J Pediatr* 2004; 144: 162-8.
28. HANCOX RJ, MILNE BJ, POULTON R, et al. Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. *Am J Respir Crit Care Med* 2005; 171: 440-5.
29. VIEIRA VJ, RONAN AM, WINDT MR, TAGLIAFERRO AR. Elevated atopy in healthy obese women. *Am J Clin Nutr* 2005; 82: 504-9.
30. 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* 2001; 56: 835-8.