

# Leptin and asthma in overweight children at 12 years of age

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Obesity is suggested as a risk factor for asthma, but the mechanisms are unclear. The relationship between obesity and asthma has not been considered in children born with very low-birth weight (VLBW). We hypothesized that overweight was a contributing factor for asthma in VLBW children, and that leptin and leptin-associated cytokines might play roles in overweight-related asthma. Seventy-four VLBW and 64 normal birth weight (NBW) children participated in a 12-yr follow up study assessing asthma and allergy. Twenty-seven (12 VLBW) of the 138 children were overweight according to the proposed international definition. The diagnosis of current asthma was made by a pediatrician. Serum levels of leptin and interferon (IFN)- $\gamma$  were analyzed by enzyme-linked immunosorbent assay (ELISA). Leptin levels were considerably higher in the overweight than in the non-overweight children (median value: 18.1 vs. 2.8 ng/ml,  $p < 0.001$ ). In the overweight children, current asthmatics had twice as high levels of leptin as children without current asthma (median value: 30.8 vs. 14.3 ng/ml,  $p = 0.14$ ), but this was not the case in the non-overweight children. IFN- $\gamma$  was more often detected in the overweight than in the non-overweight children (61% vs. 12%,  $p < 0.001$ ), and there was a positive correlation between the levels of leptin and the levels of IFN- $\gamma$  ( $Rho = 0.40$ ,  $p < 0.001$ ). In the VLBW group, the overweight children had a significantly increased risk for current asthma compared with the non-overweight children after adjustment for the neonatal risk factors [adjusted odds ratio (OR) 5.8, 95% confidence interval (CI): 1.2–27]. Thus, overweight was associated with asthma in the VLBW children. Our hypothesis remained that leptin might be involved in the pathogenesis of asthma in the overweight children, and IFN- $\gamma$  might be a pathway in the process of leptin-induced inflammation.

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Prospective studies have suggested obesity as a risk factor for asthma (1–4), but the mechanisms are not yet clear. It has been hypothesized that the biologic activities of adipose tissue, such as leptin, may in obese individuals play a role in the pathogenesis of obesity-related asthma (5). Leptin is an adipocyte-derived hormone of the long chain helical cytokine family and an *ob* gene product (6). The circulating concentration of leptin is positively correlated with body fat mass (7). Leptin has recently been suggested to have an important function: up-regulation of

inflammatory immune responses, which may provide a common pathogenetic mechanism that contributes to several of the major complications of obesity (8). For example, leptin stimulates the release of proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)- $\alpha$  from the adipose tissue (9, 10). Circulating IL-6 further stimulates the production of acute phase protein, such as C-reactive protein from the liver (11, 12) leading to an inflammatory state in obese subjects (13, 14). Leptin also promotes Th<sub>1</sub> immune responses with secretion

of interferon (IFN)- $\gamma$  (6, 15), a strong proinflammatory cytokine (16, 17). Enhanced secretion of IFN- $\gamma$ -induced inflammatory markers, such as nitric oxide and prostaglandin E<sub>2</sub>, has been observed after leptin stimulation in murine macrophages (18). Leptin is an important cytokine for the adverse influence of body fatness on chronic inflammatory disorders, such as cardiovascular diseases (19). Asthma is recognized as a chronic inflammatory disease in the airways (20), but the role of leptin in asthma development in obese subjects has been less studied. In animal models, serum leptin modulates the level of macrophage inflammatory protein in bronchoalveolar lavage fluid, suggesting a contributing effect of leptin on asthma development in obese (21). High levels of circulating leptin are associated with impaired lung function in human (22). Thus, leptin can be assumed to play a pathologic role in asthma in obese subjects.

Very low-birth weight (VLBW) is associated with the development of asthma in children (23–25). An early catch-up growth and subsequent childhood obesity in VLBW children have been suggested to contribute to the pathogenesis of many chronic inflammatory diseases (26). However, the relationship between obesity and asthma has not been considered in detail in children born with VLBW.

We thus hypothesized that overweight was an important contributing factor for asthma in VLBW children, and that the adipose-derived hormone leptin and leptin-associated proinflammatory cytokines, such as IL-6, TNF- $\alpha$ , and IFN- $\gamma$ , might be involved in asthma in overweight children.

## Methods

### Subjects

A VLBW group included all live-born infants with a birth weight  $\leq 1500$  g born between February 1, 1987 and April 30, 1988 at hospitals in the southeastern region of Sweden (27). All 86 VLBW infants who survived the first 48 h were recruited. A full-term infant with a normal birth weight (NBW) ( $\geq 2500$  g) next in order to the index child with the same sex and parity was enrolled as a control at the hospital where the VLBW infant was born or should have been born. Seventy-four (86%) of the 86 VLBW and 64 (74%) of the 86 NBW children participated in a follow up investigation assessing asthma and allergy at 12 yr of age (25). Twelve (16%) of the 74 VLBW and 15 (23%) of the 64 NBW children were overweight according to the proposed

international definition for child overweight (28). A child whose body mass index (BMI) (weight/height<sup>2</sup>, kg/m<sup>2</sup>) was more than the international cut-off value for overweight specified by age and sex was considered as being overweight (e.g., the cut-off value of BMI was 21.6 for boys and 22.1 for girls at 12.5 yr of age) (28).

### History of disease, symptoms, and diagnoses

Parents completed validated questionnaires developed by the International Study of Asthma and Allergies in Childhood (ISAAC) on asthmatic and allergic diseases. Symptoms related to asthma, i.e., a history of wheeze and current wheeze during the previous 12 months, were based on affirmative answers to specific questions on wheezing in the chest. A history of asthma was elicited by a combination of several questions on symptoms. Current asthma during the past 12 months as a clinical diagnosis of asthma was made by one of three pediatricians according to the history of the disease, physical examination, and lung function results (25).

### Spirometric measurements and hypertonic saline provocation tests

The methods of spirometry and hypertonic saline provocation tests have previously been described in detail (25). Spirometry was tested using a MasterScope spirometer (Jaeger, Germany) according to the recommendations of the American Thoracic Society Statement on Standardization of Spirometry. Flow-volume curves were performed for forced expiratory volume in 1 s (FEV<sub>1</sub>), forced expiratory volume in 1 s as a percentage of forced vital capacity (FEV<sub>1</sub>%), forced expiratory flow at 75% of forced vital capacity (FEF<sub>75</sub>), and maximal mid-expiratory flow (MMEF). Hypertonic saline (4.5%) was nebulized. The exposure time was increased progressively from 30 s to 1, 2, 4, and 8 min each, with a maximal total inhalation period of 15.5 min. The challenge test was considered positive when the decline in FEV<sub>1</sub> was more than 15%.

### Skin prick tests and IgE antibody analyses

Skin prick tests were performed in duplicate on the forearms using extracts of birch and timothy pollen, dander of cat, dog and horse, *Dermatophagoides pteronyssinus*, *D. farinae* and *Alternaria* (ALK, Hørsholm, Denmark) (25). In brief, histamine 10 mg/ml and 50% glycerin were

used as positive and negative controls. The size of a wheal was recorded as the mean of the widest diameter and the diameter perpendicular to its mid-point. A mean diameter of 3 mm or more of the duplicate wheals was regarded as positive. The presence of immunoglobulin E (IgE) antibodies to a panel of inhalant allergens was determined by UniCAP<sup>®</sup> Phadiatop<sup>®</sup> assay (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden).

#### Analyses of serum leptin and cytokines

Venous blood samples were drawn from 127 (including 23 overweight children) of the 138 children. The blood was allowed to clot and then centrifuged. The serum samples were transferred and stored in aliquots at  $-70^{\circ}\text{C}$  for later analyses. The serum levels of leptin, IL-6, and TNF- $\alpha$  were analyzed with commercially available ELISA kits (Linco Research, Inc., St Charles, MI, USA for leptin; R&D Systems, Oxford, UK for IL-6 and TNF- $\alpha$ ) according to the manufacturers' instructions. The sensitivity limit for quantitative determination of serum leptin, IL-6, and TNF- $\alpha$  was 1 ng/ml, 0.3 pg/ml, and 0.5 pg/ml respectively. The serum levels of IFN- $\gamma$  and IL-4 were also analyzed by ELISA, as described by Böttcher et al. (29). The sensitivity limit for quantitative determination was 15.6 pg/ml for IFN- $\gamma$  and 3.9 pg/ml for IL-4.

#### Statistical analyses

The VLBW and the NBW groups were merged when the levels of leptin and cytokines, such as IFN- $\gamma$ , IL-4, IL-6, and TNF- $\alpha$  were analyzed between the overweight and non-overweight children. The Mann-Whitney U-tests in STAT VIEW 5.0 for Macintosh (Abacus Concepts, Inc., Berkeley, CA, USA) were used to compare the levels of leptin, IFN- $\gamma$ , IL-4, IL-6, and TNF- $\alpha$  respectively between two independent groups because of the non-normal distribution of these parameters. Spearman rank correlation tests were employed to assess the correlations between the levels of leptin and the levels of IFN- $\gamma$ , IL-4, IL-6, and TNF- $\alpha$ . Crude odds ratios (ORs) and 95% confidence intervals (CIs) of being overweight for asthma symptoms and asthma diagnoses were calculated in children born with VLBW. Multiple logistic regression was employed to analyze being overweight as an independent contributing factor for current asthma in the VLBW children. Chi-square tests were used to compare categorical variables and the Fisher's exact tests were used when the

expected frequency for any cell was  $<5$ . The ANOVA unpaired t-tests were used to compare numeric variables of normal distribution between two independent groups.

#### Ethical aspects

The study was approved by the Human Research Ethics Committee of the Medical Faculty at Linköping University. All parents of the participating children gave their informed consent.

#### Results

The serum levels of leptin were considerably higher in the overweight than in the non-overweight children, with a median value of 18.1 ng/ml (10–90th percentile: 7.6–33.9) vs. 2.8 ng/ml (10–90th percentile: 1.1–11.1) ( $p < 0.001$ ) (Fig. 1). Female sex ( $p < 0.001$ ), high pubertal stage (by Tanner score,  $p < 0.05$ ), family history of allergy (at least one of the family members having or having had asthma and/or other allergic diseases,  $p = 0.07$ ) and current passive smoke (at least one of the family members smoking  $\geq 1$  cigarette/day during the previous 12 months,  $p = 0.06$ ) also seemed to be associated with high serum levels of leptin, but not age, inhaled steroids or birth weight. However, there were no significant differences between the overweight and non-overweight children in sex distribution, pubertal stage or proportion of current passive smoke (Table 1). More overweight children had a family history of allergy than the non-overweight children (Table 1). Higher levels of leptin remained in the overweight compared with the non-over-

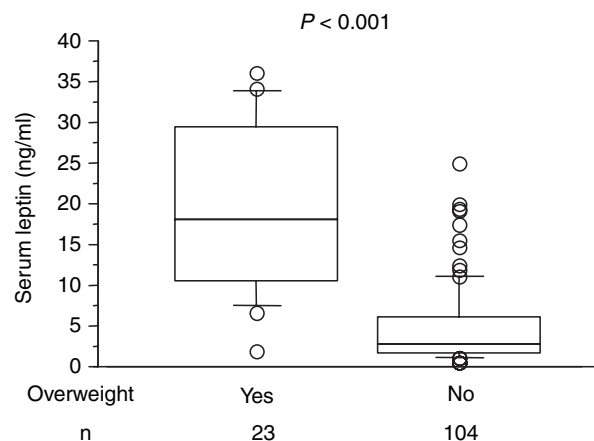


Fig. 1. Comparison between serum levels of leptin in the overweight and non-overweight children. Mann-Whitney U-test was applied.

Table 1. Potential leptin-influencing factors among the overweight and non-overweight children

|                                      | Overweight (N = 23) |             |         | Non-overweight (N = 104) |             |         | p-Value |
|--------------------------------------|---------------------|-------------|---------|--------------------------|-------------|---------|---------|
|                                      | Yes (n = 5)         | No (n = 18) | p-Value | Yes (n = 11)             | No (n = 91) | p-Value |         |
| Age (years)                          | 12.7 ± 0.2          | 12.6 ± 0.2  | 0.64    | 12.8 ± 0.4               | 12.6 ± 0.3  | 0.14    | 0.74    |
| Body mass index (kg/m <sup>2</sup> ) | 24.4 ± 1.4          | 24.1 ± 2.1  | 0.68    | 18.0 ± 2.1               | 17.9 ± 2.0  | 0.74    | <0.001  |
| Pubertal stage (hair)                | 2.0 ± 0.7           | 2.7 ± 1.2   | 0.14    | 2.3 ± 1.1                | 2.5 ± 1.0   | 0.53    | 0.32    |
| Girls (%)                            | 20                  | 39          | 0.61    | 45                       | 48          | 0.91    | 0.44    |
| Inhaled steroid (%)                  | 20                  | 4           | <0.001  | 40                       | 4           | <0.001  | >0.99   |
| Family history of allergy (%)        | 80                  | 83          | >0.99   | 82                       | 63          | 0.20    | 0.05    |
| Current passive smoke (%)            | 40                  | 35          | >0.99   | 55                       | 37          | 0.19    | 0.87    |
| Very low-birth weight (%)            | 80                  | 48          | 0.16    | 64                       | 55          | 0.75    | 0.54    |
|                                      |                     | 39          |         |                          | 54          |         |         |

Mean ± s.d. shown for numeric variables. Unpaired t-tests were used to compare numeric variables between two independent groups. Chi-square tests were used to compare nominal variables and the Fisher's exact tests were used when the expected frequency for any cell was <5. Family history of allergy: at least one of the family members having or having had asthma and/or other allergic diseases. Current passive smoke: at least one of the family members smoking ≥1 cigarette/day during the previous 12 months.

weight children after adjustment for family history of allergy ( $p < 0.001$ ), and there was no interaction between overweight and family history of allergy. In the overweight children, the levels of leptin were twice as high in children with current asthma as in children without current asthma [median and 10–90th percentile: 30.8 ng/ml (10.3–34.2) vs. 14.3 ng/ml (7.0–33.4),  $p = 0.14$ ] (Fig. 2). This was not the case, however, in the non-overweight children [median and 10–90th percentile: 3.4 ng/ml (1.0–11.8) vs. 2.8 ng/ml (1.1–11.1),  $p = 0.81$ ]. Sex distribution, pubertal stage, proportion of family history of

allergy, proportion of current passive smoke and BMI were similar in children with and without current asthma in both the overweight and non-overweight children (Table 1).

Interferon- $\gamma$  was detected in 61% (14 of 23) of the overweight children, compared with 12% (11 of 89) of the non-overweight children ( $p < 0.001$ ). The rate of detectable IFN- $\gamma$  did not differ significantly in children with and without current asthma, however, either in the overweight children (80% vs. 56%,  $p = 0.61$ ) or in the non-overweight children (29% vs. 11%,  $p = 0.21$ ). There was a positive correlation between the levels of leptin and the levels of IFN- $\gamma$  ( $Rho = 0.40$ ,  $p < 0.001$ ), but no correlation between the levels of leptin and the levels of IL-4, IL-6, or TNF- $\alpha$ . The levels of IL-4, IL-6, and TNF- $\alpha$  were similar in the overweight and non-overweight children [median and 10–90th percentile: IL-4, 11.7 pg/ml (2.0–27.7) vs. 10.8 pg/ml (2.0–25.2),  $p = 0.51$ ; IL-6, 0.70 pg/ml (0.38–2.3) vs. 0.62 pg/ml (0.38–2.9),  $p = 0.65$ , and TNF- $\alpha$ , 3.97 pg/ml (1.91–10.7) vs. 3.40 pg/ml (1.73–14.7),  $p = 0.81$ ]. The levels of IL-4, IL-6 and TNF- $\alpha$  were also similar in children with and without current asthma, irrespective of overweight.

There was a similar prevalence of positive skin prick tests and positive Phadiatop<sup>®</sup> in the overweight and non-overweight children (15% vs. 13%,  $p = 0.72$  and 32% vs. 27%,  $p = 0.66$ , respectively). Current asthma tended to be associated with positive skin prick tests in the

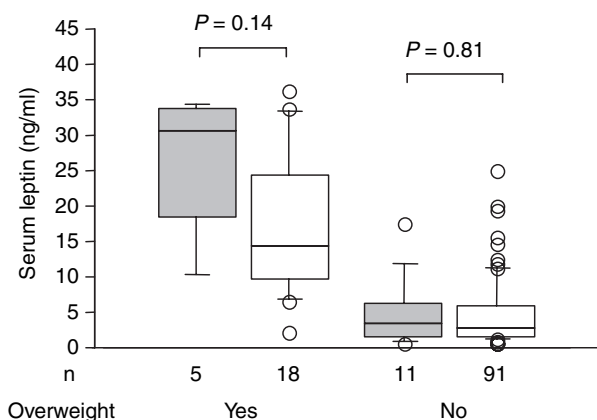


Fig. 2. Leptin in relation to current asthma in the overweight and non-overweight children. Shaded boxes indicate children with current asthma and open boxes indicate children without current asthma. Mann-Whitney U-tests were applied.

non-overweight children ( $p = 0.07$ ), but not in the overweight children ( $p = 0.92$ ). However, current asthma was not associated with positive Phadiatop<sup>®</sup> in either group of children ( $p = 0.37$  for both).

In the VLBW group, the overweight children had similar birth weight, gestational age, proportion of the administration of neonatal mechanical ventilation and neonatal oxygen supplementation as the non-overweight children (Table 2), and there were no significant differences in age, pubertal stage, and sex distribution in the two groups of children at the 12-yr investigation (Table 2).

Among the VLBW children, children with overweight had a significantly increased risk for current asthma compared with the non-overweight children, with an OR of 5.5 (95% CI: 1.3–22.2) (Table 3). Oxygen supplementation during

the neonatal period was previously revealed as the only significant risk factor for the development of asthma in the VLBW children after adjustment for several neonatal risk factors (25). Multiple logistic regression showed that both oxygen supplementation during the neonatal period (adjusted OR 6.6, 95% CI: 1.2–35) and overweight (adjusted OR 5.8, 95% CI: 1.2–27) contributed independently to current asthma in the VLBW children. In addition, FEV<sub>1</sub>% was significantly lower in the overweight than in non-overweight children (Table 3). The significance disappeared, however, after the adjustment for current asthma. The values of other spirometric parameters (FEV<sub>1</sub>, FEF<sub>75</sub>, and MMEF) did not differ significantly in the overweight and non-overweight children, or did the prevalence of positive hypertonic saline provocation tests (Table 3).

## Discussion

Considerably increased levels of serum leptin were observed in the overweight children compared with non-overweight children. Interestingly, among the overweight children, those with current asthma had twice as high levels of leptin, although not statistically significant ( $p = 0.14$ ), as those without current asthma despite of similar BMI. The BMI is an acceptable index for overweight, but its correlation with body fat mass is weak. Unfortunately, we did not have data on body fat mass. Therefore, we could not correlate the serum leptin level with fat mass in the overweight children. Based on our results, our hypothesis remained that leptin among other possible factors might play a role in the pathogenesis of asthma in overweight children. The

Table 2. Characteristics of children with and without overweight born with very low-birth weight

|                                        | Overweight<br>(N = 12) | Non-overweight<br>(N = 62) | p-Value |
|----------------------------------------|------------------------|----------------------------|---------|
| Birth weight (g)                       | 1241.3 ± 231.5         | 1196.8 ± 208.4             | 0.51    |
| Gestational age (weeks)                | 30.7 ± 2.5             | 30.8 ± 2.6                 | 0.91    |
| Neonatal mechanical ventilation (n, %) | 2 (17%)                | 11 (18%)                   | >0.99   |
| Neonatal oxygen supplement (n, %)      | 7 (58%)                | 30 (48%)                   | 0.53    |
| Age (years)                            | 12.6 ± 0.2             | 12.6 ± 0.3                 | 0.62    |
| Boys (n, %)                            | 9 (75%)                | 35 (56%)                   | 0.34    |
| Body mass index (kg/m <sup>2</sup> )   | 23.5 ± 1.1             | 17.4 ± 1.8                 | <0.001  |
| Pubertal stage (hair)                  | 2.2 ± 0.8              | 2.5 ± 1.0                  | 0.28    |

Mean ± s.d. shown for numeric variables. Unpaired t-tests were used to compare numeric variables between the overweight and non-overweight children. Chi-square tests were used to compare nominal variables and the Fisher's exact tests were used when the expected frequency for any cell was <5.

Table 3. Comparisons between the overweight and non-overweight children born with very low-birth weight regarding asthma symptoms and diagnosis and lung function tests

|                                      | Overweight (N = 12) |                | Non-overweight (N = 62) |             | p-Value |
|--------------------------------------|---------------------|----------------|-------------------------|-------------|---------|
|                                      | n (%)               | OR (95% CI)    | n (%)                   | OR          |         |
| History of wheeze                    | 6 (50)              | 2.3 (0.6–8.0)  | 19 (31)                 | 1.0         | 0.32    |
| Current wheeze                       | 3 (25)              | 2.6 (0.5–12.1) | 7 (11)                  | 1.0         | 0.35    |
| History of asthma                    | 5 (42)              | 3.3 (0.8–12.4) | 11 (18)                 | 1.0         | 0.12    |
| Current asthma                       | 5 (42)              | 5.5 (1.3–22.2) | 7/61 (11)               | 1.0         | 0.02    |
| Positive bronchial provocation tests | 5/11 (45)           | 2.0 (0.5–7.4)  | 17/57 (30)              | 1.0         | 0.32    |
| FEV <sub>1</sub> /pred.              |                     | 0.95 ± 0.10    |                         | 0.92 ± 0.12 | 0.46    |
| FEF <sub>75</sub> /pred.             |                     | 0.83 ± 0.24    |                         | 0.94 ± 0.27 | 0.22    |
| MMEF/pred.                           |                     | 0.86 ± 0.27    |                         | 0.85 ± 0.21 | 0.87    |
| FEV <sub>1</sub> %                   |                     | 87.2 ± 5.1     |                         | 92.5 ± 8.2  | 0.04    |

OR, odds ratio; CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 s; FEF<sub>75</sub>, force expiratory flow at 75% of forced vital capacity; MMEF, maximal mid-expiratory flow; FEV<sub>1</sub>%, forced expiratory volume in 1 s as a percentage of forced vital capacity; pred., predicted value.

Unpaired t-tests were used to compare numeric variables between the overweight and non-overweight children. Chi-square tests were used to compare nominal variables and the Fisher's exact tests were used when the expected frequency for any cell was <5.

non-statistical significance was most possibly due to a small sample size.

Leptin is hypothesized to promote Th<sub>1</sub> immune responses with secretion of the proinflammatory cytokine IFN- $\gamma$  (6). Malnutrition-related hypo-leptinemia is associated with reduced Th<sub>1</sub> responses (15). The high rate of detectable IFN- $\gamma$  in the overweight children who had high levels of leptin, and the positive correlation between the levels of leptin and the levels of IFN- $\gamma$  in our study partly supported this hypothesis. Leptin has also been reported to increase the expression and secretion of IFN- $\gamma$ -inducible protein (IP-10) in human peripheral blood mononuclear cells (30). Enhanced secretion of IFN- $\gamma$ -induced inflammatory markers, such as nitric oxide and prostaglandin E<sub>2</sub> and their respective inducible enzymes (nitric oxide synthase and cyclo-oxygenase-2) is observed after leptin stimulation in murine macrophages, and the effect is synergized with the presence of IFN- $\gamma$  (18). Thus, interferon- $\gamma$  can be a possible pathway in the process of leptin-induced inflammation.

Interferon- $\gamma$  is a strong proinflammatory cytokine (16, 17) and is involved in the inflammatory process of asthma in adults (31). Interferon- $\gamma$ -producing T cells are more abundant in bronchoalveolar lavage fluid from atopic asthmatic children than atopic non-asthmatic children and controls, indicating that the proinflammatory activities of IFN- $\gamma$  may also play a role in the pathogenesis of childhood asthma (32). Mito et al. have recently observed that obese mice with ovalbumin-induced asthma show an increase of IFN- $\gamma$  production in splenocytes with phytohemagglutinin stimulation, but a decline of ovalbumin-specific IgE (33). Their results suggest that enhanced IFN- $\gamma$  may partly be involved in the pathophysiology of asthma in human obesity, rather than IgE-mediated atopic responses. To date, there has been no strong evidence demonstrating the relationship between obesity and atopy in epidemiologic studies (34). Our study showed an increase in IFN- $\gamma$ , but not in IL-4, and a lack of association between current asthma and positive skin prick tests in the overweight children, suggesting that overweight-related asthma might not be mediated by Th<sub>2</sub>-skewed atopic inflammation. The lack of a significance of IFN- $\gamma$  between children with and without current asthma in the overweight children in our study could also be due to small sample size.

Leptin can also stimulate the release of proinflammatory cytokines IL-6 and TNF- $\alpha$  from the adipose tissue (9, 10). Circulating IL-6 stimulates

the production of acute-phase proteins from the liver (11, 12) leading to an inflammatory state in obese subjects (13, 14). Besides, IL-6 has local effects on fibrogenesis and airway remodeling (35). TNF- $\alpha$  can enhance adhesion molecule expression on endothelial cells and facilitate the migration of inflammatory cells to the airway wall (36). Serum levels of IL-6 and TNF- $\alpha$  are elevated in obese adults (37, 38). However, we did not find significant differences in IL-6 and TNF- $\alpha$  between the overweight and non-overweight children. Moderately high levels of BMI in our children could be the explanation for the lack of difference. Therefore, interleukin-6 and TNF- $\alpha$  as possible pathways in the process of leptin-induced inflammation was limited.

In the VLBW children, oxygen supplement during the neonatal period was identified to be the only significant neonatal risk factor for childhood asthma in our previous study (25). The present study showed that overweight at 12 yr of age was another important factor associated with current asthma in the VLBW children. The similar FEV<sub>1</sub>% in the overweight and non-overweight children after adjustment for current asthma indicated that overweight *per se* was not associated with small airway size, at least in the VLBW children. Whether childhood overweight is associated with an early catch-up growth in children born with VLBW and among these two, which is the most important risk factor for the development of asthma, cannot be answered in the present study and need to be further investigated.

In summary, overweight was one of the important contributing factors for asthma in the VLBW children. The adipose-derived hormone leptin could be hypothesized to be involved in the pathogenesis of asthma in the overweight children, and IFN- $\gamma$  might be a pathway in the process of leptin-induced inflammation.

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