

ORIGINAL ARTICLE

Role of gender disparity of circulating high-sensitivity C-reactive protein concentrations and obesity on asthma in Taiwan

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Summary

Background Several studies have suggested that the association between obesity and asthma may be stronger in females than in males, but the reason is still unclear.

Objective The aim of this study was to investigate whether differences in high-sensitivity C-reactive protein (hs-CRP) levels explain why obesity is associated with asthma in females but not in males.

Methods This study prospectively enrolled 754 subjects ≥ 18 years old from hospital-based asthma patients and population-based controls. We measured adiposity factors [body mass index (BMI), waist circumference and waist-hip ratio], hs-CRP and total IgE levels.

Results After adjusting for potential confounding factors, we found a significant association between BMI and asthma in females with a significant interaction of gender and BMI on asthma ($\chi^2 = 10.2$, $P = 0.004$). If hs-CRP was added to the logistic model, the interaction was attenuated but still significant ($\chi^2 = 7.02$, $P = 0.03$). After adjusting for BMI, we did not find that circulating hs-CRP concentrations were significantly associated with asthma in males and females.

Conclusion We found that BMI was associated with asthma in females, but our results do not support the suggestion that hs-CRP levels contribute significantly to the link between obesity and asthma with respect to gender disparity.

Keywords asthma, gender, hs-CRP, obesity

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Introduction

Several studies have suggested an association between obesity and asthma, and this effect is particularly strong in females [1–10]. Asthma occurs frequently in boys before puberty; this gender preference changes after puberty, and adult females tend to have more severe and often difficult to control symptoms [11]. The underlying mechanism that drives the relationship between obesity and asthma in gender disparity is still unknown.

Asthma is a complex disease that is caused by acute and chronic inflammation in the airways. Asthma evokes chronic inflammatory reactions that are mediated by a number of cytokines, chemokines and other mediators. A highly sensitive assay for C-reactive protein (CRP) was

developed to detect low-grade system inflammation and has been used in several chronic inflammatory disorders, including cardiovascular diseases [12–14] and diabetes mellitus [15–18].

Michel et al. [19] found that CRP levels and inflammatory markers increase during the acute inhalation of endotoxin in asthmatic patients. Circulating high-sensitivity CRP (hs-CRP) levels may be positively associated with airflow obstruction, airway inflammation and impaired lung function [20, 21]. Butland et al. [22] found that hs-CRP levels were positively correlated with BMI and smoking and increased significantly in those patients with non-atopic asthma.

Several studies have reported that hs-CRP had a gender-specific effect on diabetes risk [15–18, 23]. The first

objective of the current study was to investigate whether there really was a difference in the association between BMI and asthma relative to gender. The second aim was to examine whether CRP levels could explain the association of obesity with asthma in either gender. To our knowledge, this is the first study to investigate the role of gender differences in circulating hs-CRP on adult asthma.

Methods

Subjects

Asthmatic group. From August 2006 to August 2008, we recruited 405 asthmatic adults aged at least 18 years of age from the out-patient lists of two medical centres: the Division of Chest Medicine of Kaohsiung Medical University and the Division of Pulmonary and Critical Care Medicine of Chang-Gung Memorial Hospital in southern Taiwan. Asthma was diagnosed by interviewing all subjects with chest physicians according to the Global Initiative on Asthma guidelines [24]. Five asthmatic patients refused to provide a blood sample and an assessment of body parameters (the response rate was 98.8%, 400/405). We excluded 28 asthmatic patients with emphysema, chronic airway obstruction, tuberculosis, pneumonia or cancer. Thus, a total of 372 asthmatics were further analysed for body parameters and cytokines.

Control group. From August 2006 to August 2008, community controls were collected from a health investigation conducted at local health stations by advertising in two communities in southern Taiwan. We expected to recruit 600 community controls (≥ 18 years old). A total of 545 control adults (the response rate 90.8%, 545/600) agreed to an assessment of body parameters and provided blood samples. Of the community controls, 42 were excluded from this study because they had experienced at least one of the following: physician-diagnosed asthma, chronic airway obstruction, emphysema, tuberculosis, pneumonia or cancer. Finally, 382 adults were selected in the order they were recruited out of 503 eligible subjects. The protocol was approved by the Institutional Review Board of Chang-Gung Memorial Hospital and Kaohsiung Medical University. Informed written consent was obtained from all study subjects.

Phenotype and adiposity-parameters analysis

Each subject completed a questionnaire, including questions about demographics, cigarette and alcohol use, previous and current occupational history, medical history (history of asthma, atopic dermatitis, allergic rhinitis, hypertension and diabetes mellitus diagnosed by a physician), and environmental exposure. The total plasma IgE level was measured using a solid-phase, chemilumines-

cent immunometric assay (IMMULITE 2000 Analyzer, Diagnostic Products Corporation, Los Angeles, CA, USA). The body parameters measured included body weight, height, body mass index (BMI) (kg/m^2), waist and hip circumferences and waist-hip ratio (WHR). Height, waist and hip circumferences were measured to the nearest 0.5 centimetres, and body weight was measured to the nearest 0.1 kg.

We measured and categorized BMI, waist circumference and WHR [25] to define the degree of obesity, according to the following gender-specific international criteria. BMI criteria: normal range ($< 25 \text{ kg/m}^2$), overweight ($\geq 25\text{--}30 \text{ kg/m}^2$) and obese ($\geq 30 \text{ kg/m}^2$); waist circumference criteria: normal ($< 94 \text{ cm}$ for males and $< 80 \text{ cm}$ for females), overweight ($\geq 94\text{--}102 \text{ cm}$ for males and $\geq 80\text{--}88 \text{ cm}$ for females) and obese ($\geq 102 \text{ cm}$ for males and $\geq 88 \text{ cm}$ for females); WHR criteria: normal (≤ 1.0 for males and ≤ 0.85 for females) and obese (> 1.00 for males and > 0.85 for females).

High-sensitivity C-reactive protein levels

Plasma was stored at -70°C before hs-CRP levels were assayed. The hs-CRP level was measured using a solid-phase, chemiluminescent immunometric assay (IMMULITE/IMMULITE 1000 Analyzer, Diagnostic Products Corporation). The lowest level of hs-CRP detectable by this assay is 0.1 mg/L.

Statistical analysis

The χ^2 -test was used to evaluate the percentage differences in risk factors for asthma and control groups. The *t*-test was performed to assess the mean differences between the two groups. Plasma hs-CRP and total IgE levels were non-normally distributed in this study; thus, we present median and interquartile ranges and used the Mann-Whitney *U*-test to compare group differences (Table 1). Total IgE and hs-CRP levels were logarithmically transformed before controlling for confounding factors. Adjusted odds ratios (aOR) and 95% confidence intervals (CIs) for each risk factor of asthma were calculated by logistic regression, after adjusting for gender, age, smoking status and forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio. Trend tests were assessed by entering cross-categorized variables as a continuous variable by logistic regression models (Tables 2 and 3). We performed statistical analysis using the software package SPSS 14.0.

Results

Table 1 presents the descriptive characteristics of the asthma and control groups. The mean age and gender distribution of the asthmatic adults were similar to the

Table 1. Descriptive characteristics of allergies and adiposity measured in asthmatic and control adults

Variables	Asthma	Control	P-value
No.	372	382	
Male/female	142/230	130/252	0.27
Age (mean±SD)	50.06±14.06	50.81±13.48	0.46
The age at first time diagnosis±SD (years)	43.32±17.03	–	–
Lung function			
FEV ₁ (% pred)	85.3±21.8	90.4±16.8	0.001
FVC (% pred)	88.4±21.9	96.3±16.9	<0.001
FEV ₁ /FVC ratio	0.97±0.13	0.96±0.11	0.24
Adiposity measures			
BMI±SD (kg/m ²)	25.14±4.16	23.77±3.41	<0.001
Waist±SD (cm)	85.42±10.99	79.41±9.97	<0.001
Hip±SD (cm)	98.94±9.01	96.13±6.84	<0.001
WHR±SD	0.86±0.09	0.83±0.07	<0.001
Hs-CRP, median (25–75%) (mg/L)*	0.82 (0.32–1.99)	0.59 (0.27–1.34)	0.004
IgE, median (25–75%) (U/mL)*	88.3 (26.5–230.5)	37.3 (15.4–117.0)	<0.001
IgE > 100 (U/mL)	175 (47.0%)	104 (28.7%)	<0.001
Hypertension (%)	90 (24.2%)	62 (16.2%)	0.02
Diabetes, %	24 (6.5%)	24 (6.3%)	0.91
Smoking status (ex or current) (%)	85 (22.8%)	59 (15.4%)	<0.001
Passive smoking (%)	98 (26.3%)	124 (32.5%)	0.08
Indoor environmental factors			
Pets (dogs, cats, birds) (%)	111 (29.8%)	81 (21.2%)	0.01
Mould in walls (%)	68 (18.3%)	62 (16.2%)	0.57
Presence of cockroaches (frequent) (%)	300 (80.6%)	346 (90.6%)	<0.001
Indoor incense burning (%)	230 (61.8%)	183 (47.9%)	<0.001

*IgE and hs-CRP levels did not meet the assumption of normal distribution; therefore, we present median and interquartile ranges and used the Mann-Whitney *U*-test to compare group differences.

BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation; WHR, waist-hip ratio.

controls. The measures of adiposity (BMI, waist and hip circumference and WHR) and hs-CRP levels in the asthmatic group were significantly higher than in the control group ($P < 0.001$ each). The frequency of environmental tobacco smoke in the asthma group was not different from the control group ($P > 0.05$). Cigarette smoking and indoor environmental factors (pets and presence of cockroaches) were different between the two groups.

After adjusting for age, smoking, FEV₁/FVC ratio and log hs-CRP, we found that the ORs in the highest tertiles of BMI increased significantly in female asthma patients (aOR = 13.83, 95% CI: 3.15–60.7) with a significant interaction of gender and BMI on asthma ($P = 0.03$). The association of obesity, measured by the BMI, with adult asthma was significantly stronger for females compared with males (interaction $P = 0.004$ and $P = 0.03$ before and after including hs-CRP levels in logistic regression, respectively). We found that the WHR and waist circumference had significant associations with asthma in females only, but they did not interact with gender on asthma after adjusting for log hs-CRP (Table 2).

After adjusting for age, gender, smoking, FEV₁/FVC ratio and BMI, we found that the highest tertile of hs-CRP was significantly associated with asthma (aOR = 1.56, 95%

CI: 1.02–2.39). An interaction between gender and hs-CRP on asthma was not observed ($P = 0.62$) (Table 3).

Discussion

There are at least five cohort studies [1–5] and five cross-sectional studies [6–10] that have reported a stronger association between BMI and asthma in females than in males. However, the biochemical mechanisms for this gender disparity are unknown. There are several interesting findings in this study. BMI, both by itself and with female gender, associated with asthma, and these associations were attenuated, but still significant, after adjusting for hs-CRP concentrations. Our findings suggested that the effect of BMI on asthma may not be mediated by hs-CRP alone, and other mechanistic pathways are probably involved in asthma pathogenesis. This study also found that hs-CRP level is associated with asthma in females, but this relationship disappeared after adjusting for BMI. These findings suggested that BMI may confound the correlation between hs-CRP and asthma, overestimating the actual association.

An assay for high-sensitivity CRP is a crucial biomarker used to detect low-grade system inflammation. Higher

Table 2. The association of adiposity measures with asthma in males and females was analysed by logistic regression models

	Men					Women		
	Total	Men		Women		Women		
BMI	Case/ control *	cOR (95% CI)	aOR1 (95% CI)	aOR2 (95% CI)	cOR (95% CI)	aOR1 (95% CI)	aOR2 (95% CI)	
Normal ($<25 \text{ kg/m}^2$)	196/246	1	1	1	1	1	1	1
Overweight ($25\text{--}29.9 \text{ kg/m}^2$)	135/123	1.38 (1.01–1.88)	1.57 (1.12–2.19)	1.51 (1.06–2.16)	0.86 (0.53–1.42)	0.98 (0.57–1.68)	1.09 (0.61–1.94)	1.79 (1.21–2.67)
Obese ($\geq 30 \text{ kg/m}^2$)	41/13	3.96 (2.06–7.56)	5.66 (2.57–12.5)	4.39 (1.94–9.94)	1.79 (0.64–5.03)	1.52 (0.52–4.46)	1.31 (0.42–4.04)	6.15 (2.61–14.5)
P for trend test		< 0.001	< 0.001	< 0.001	0.73	0.64	0.63	< 0.001
P-value for interaction of gender and BMI	0.03	0.004	0.03					< 0.001

*Dependent variable: presence of asthma. Total IgE and hs-CRP levels were logarithmically transformed before controlling as confounding factors to meet the assumption of normal distribution.

Model 1: aOR1 was adjusted for age, gender (except gender-specific models), smoking and FEV₁/FVC ratio.

Model 2: aOR2 was adjusted for variables in aOR1 plus log hs-CRP.

P-values for interaction of gender and WHR on asthma were 0.85 and 0.66 before and after adjusting for log hs-CRP (data not shown).

P-values for interaction of gender and waist circumference on asthma were 0.22 and 0.28 before and after adjusting for log hs-CRP, respectively (data not shown).

aOR, adjusted odds ratios; BMI, body mass index; cOR, crude odds ratio; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; hs-CRP, high-sensitivity C-reactive protein; 95% CI, 95% confidence intervals; WHR, waist-hip ratio.

than normal levels of hs-CRP may lead to chronic inflammatory diseases, including cardiovascular diseases, diabetes mellitus [12–18] and asthma [20, 21, 26]. Sutherland et al. [27] assessed the relationships between airway inflammation and systemic inflammation in a birth cohort of approximately 1000 individuals. However, they found no association between hs-CRP and exhaled nitric oxide. Sood et al. [28] hypothesized that the leptin level was associated with asthma in women, but the relationship disappeared after adjusting for BMI. A population-based birth cohort study did not observe the relationship between leptin and asthma in either males or females [29]. A cohort study suggested that asthma is linked with obesity in adults, but leptin does not play a significant role in this association [30]. Mai et al. [31] proposed that leptin was possibly involved as a regulatory rather than the causal mechanism of asthma pathogenesis.

Asthma is a leukotriene-related disorder. Pergola et al. [32] found that leukotriene formation and neutrophils are present in lower levels in males as compared with females. Their findings may be related to the activation of extracellular signal-regulated kinases and the suppression of leukotriene formation by androgens. These findings fit well with data supporting that females are more likely to develop asthma during adolescence [2, 5] and the reduction of asthma observed in males during puberty [11, 33]. Higher circulating hs-CRP levels also correlated with lower total testosterone and sex hormone-binding globulin (SHBG) levels in different groups, including elderly men, adolescents during puberty and postmenopausal women [34–36]. In this study, we did not measure sex hormones or SHBG levels. Prospective studies are necessary to confirm the results and include sex hormones and other inflammatory biomarkers to examine the individual contributions of these markers to asthma. In the present study, we observed that circulating hs-CRP levels were significantly higher in the obese than in the non-obese; also, several obesity-related parameters (BMI, waist circumference and WHR) had greater correlations with hs-CRP levels in females than in males (data not shown) (correlation coefficient (r): 0.21–0.42 for females and r : 0.18–0.23 for males). Therefore, obesity-related inflammation may have a stronger association with the pathogenesis of asthma in females.

Our study has several strengths. First, smoking, hs-CRP and lung function were associated with both the independent and the dependant variables and were included in multiple logistic regressions to control for potential confounding effects. Second, to assess whether hs-CRP showed a gender-disparity association with asthma, we used interaction terms instead of subgroup analyses to detect a gender difference. We did not find an interaction of hs-CRP with gender in asthma but confirmed a statistically significant interaction between BMI and gender in asthma.

Table 3. The association of hs-CRP levels with asthma in males and females was analysed by logistic regression models

		Model 1	Model 2	Model 3
Gender	Risk factor	cOR	aOR	aOR included BMI
Both				
	hs-CRP, tertile (mg/L)			
	Q1 (<0.41)	1	1	1
	Q2 (0.41–1.22)	1.01 (0.70–1.45)	1.11 (0.75–1.65)	0.95 (0.64–1.42)
	Q3 (≥1.22)	1.72 (1.19–3.26)	2.12 (1.42–3.17)	1.56 (1.02–2.39)
	<i>P</i> -value for trend test	0.003	< 0.001	0.04
Male				
	hs-CRP, tertile (mg/L)			
	Q1 (<0.41)	1	1	1
	Q2 (0.41–1.22)	1.05 (0.56–1.96)	1.21 (0.63–2.33)	1.19 (0.62–2.28)
	Q3 (≥1.22)	1.46 (0.77–2.79)	1.76 (0.88–3.52)	1.61 (0.80–3.27)
	<i>P</i> -value for trend test	0.24	0.11	0.19
Female				
	hs-CRP, tertile (mg/L)			
	Q1 (<0.41)	1	1	1
	Q2 (0.41–1.22)	0.94 (0.59–1.49)	1.03 (0.63–1.67)	0.79 (0.47–1.31)
	Q3 (≥1.22)	1.85 (1.19–2.86)	2.26 (1.38–3.70)	1.45 (0.85–2.48)
	<i>P</i> -value for trend test	0.007	0.001	0.18
<i>P</i> -value for interaction of gender and tertile of hs-CRP		0.66	0.61	0.62

Dependent variable: presence of asthma.

Model 1: cOR for hs-CRP.

Model 2: adjusted for age, gender (except gender-specific models), smoking and FEV₁/FVC ratio.

Model 3: adjusted for variables in aOR plus BMI.

Model 4: adjusted for variables in model 2 plus WHR (data not shown).

Model 5: adjusted for variables in model 2 plus waist circumference (data not shown).

The P-value for interaction of gender and tertile of hs-CRP on asthma in model 4 was 0.69 (data not shown).

The P-value for interaction of gender and tertile of hs-CRP on asthma in model 5 was 0.59 (data not shown).

aOR, adjusted odds ratios; BMI, body mass index; cOR, crude odds ratio; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; hs-CRP, high-sensitivity C-reactive protein; WHR, waist-hip ratio.

Symptoms controlled by medication use may influence the plasma hs-CRP concentrations in asthmatic patients. In previous study, serum hs-CRP levels were significantly increased in the steroid-naïve patients compared with controls and this increase was not observed in asthmatic patients who were using inhaled corticosteroids [20]. In contrast, Butland et al. [22]. detected a positive association between hs-CRP and the intake of asthma medication in patients 24 h before providing blood samples. These findings suggested that the steroid-related suppressive effect of hs-CRP levels is still controversial. In conclusion, BMI was associated with asthma in females, and asthma interacted with both gender and BMI. The findings did not provide evidence in support of a major role for hs-CRP in linking obesity and asthma in females.

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References

- Beckett WS, Jacobs DR Jr, Yu X, Iribarren C, Williams OD. Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Respir Crit Care Med* 2001; **164**:2045–50.
- Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthma like symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med* 2001; **163**:1344–9.
- 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* 2002; **155**:191–7.
- Guerra S, Sherrill DL, Bobadilla A, Martinez FD, Barbee RA. The relation of body mass index to asthma, chronic bronchitis, and emphysema. *Chest* 2002; **122**:1256–63.
- 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.
- Seidell JC, de Groot LC, van Sonsbeek JL, Deurenberg P, Hautvast JG. Associations of moderate and severe overweight with self-reported illness and medical care in Dutch adults. *Am J Public Health* 1986; **76**:264–9.

- 7 Figueroa-Munoz JI, Chinn S, Rona RJ. Association between obesity and asthma in 4–11 year old children in the UK. *Thorax* 2001; **56**:133–7.
- 8 von Kries R, Hermann M, Grunert VP, von Mutius E. Is obesity a risk factor for childhood asthma? *Allergy* 2001; **56**:318–22.
- 9 Chen Y, Dales R, Krewski D, Breithaupt K. Increased effects of smoking and obesity on asthma among female Canadians: the national population health survey, 1994–1995. *Am J Epidemiol* 1999; **150**:255–62.
- 10 Huang SL, Shiao G, Chou P. Association between body mass index and allergy in teenage girls in Taiwan. *Clin Exp Allergy* 1999; **29**:323–9.
- 11 Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008; **63**:1418–27.
- 12 Pai JK, Pischon T, Ma J *et al*. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med* 2004; **351**:2599–610.
- 13 Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; **336**:973–9.
- 14 Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; **347**:1557–65.
- 15 Han TS, Sattar N, Williams K *et al*. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico city diabetes study. *Diabetes Care* 2002; **25**:2016–21.
- 16 Nakanishi S, Yamane K, Kamei N, Okubo M, Kohno N. Elevated C-reactive protein is a risk factor for the development of type 2 diabetes in Japanese Americans. *Diabetes Care* 2003; **26**:2754–7.
- 17 Snijder MB, Dekker JM, Visser M *et al*. Prospective relation of C-reactive protein with type 2 diabetes: response to Han *et al*. *Diabetes Care* 2003; **26**:1656–7; author reply 7–8.
- 18 Doi Y, Kiyohara Y, Kubo M *et al*. Elevated C-reactive protein is a predictor of the development of diabetes in a general Japanese population: the hisayama study. *Diabetes Care* 2005; **28**:2497–500.
- 19 Michel O, Ginanni R, Le Bon B *et al*. Inflammatory response to acute inhalation of endotoxin in asthmatic patients. *Am Rev Respir Dis* 1992; **146**:352–7.
- 20 Takemura M, Matsumoto H, Niimi A *et al*. High sensitivity C-reactive protein in asthma. *Eur Respir J* 2006; **27**:908–12.
- 21 Rasmussen F, Mikkelsen D, Hancox RJ *et al*. High-sensitive C-reactive protein is associated with reduced lung function in young adults. *Eur Respir J* 2009; **33**:382–8.
- 22 Butland BK, Strachan DP, Rudnicka AR. C-reactive protein, obesity, atopy and asthma symptoms in middle-aged adults. *Eur Respir J* 2008; **32**:77–84.
- 23 Hu G, Jousilahti P, Tuomilehto J *et al*. Association of serum C-reactive protein level with sex-specific type 2 diabetes risk: a prospective finnish study. *J Clin Endocrinol Metab* 2009; **94**:2099–105.
- 24 GINA. Global initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report. National Institutes of Health, Bethesda National Heart Lung and Blood Institute, 1995: publication number 95–3659.
- 25 World Health Organization. *Obesity: preventing and managing the global epidemic: report of a WHO consultation on obesity*. Geneva: World Health Organization, 1997.
- 26 Qian FH, Zhang Q, Zhou LF *et al*. High-sensitivity C-reactive protein: a predicative marker in severe asthma. *Respirology* 2008; **13**:664–9.
- 27 Sutherland TJ, Taylor DR, Sears MR *et al*. Association between exhaled nitric oxide and systemic inflammatory markers. *Ann Allergy Asthma Immunol* 2007; **99**:534–9.
- 28 Sood A, Ford ES, Camargo CA Jr Association between leptin and asthma in adults. *Thorax* 2006; **61**:300–5.
- 29 Sutherland TJ, Sears MR, McLachlan CR, Poulton R, Hancox RJ. Leptin, adiponectin, and asthma: findings from a population-based cohort study. *Ann Allergy Asthma Immunol* 2009; **103**:101–7.
- 30 Jartti T, Saarikoski L, Jartti L *et al*. Obesity, adipokines and asthma. *Allergy* 2009; **64**:770–7.
- 31 Mai XM, Chen Y, Krewski D. Does leptin play a role in obesity–asthma relationship? *Pediatr Allergy Immunol* 2009; **20**:207–12.
- 32 Pergola C, Dodt G, Rossi A *et al*. ERK-mediated regulation of leukotriene biosynthesis by androgens: a molecular basis for gender differences in inflammation and asthma. *Proc Natl Acad Sci USA* 2008; **105**:19881–6.
- 33 Almqvist C, Worm M, Leynaert B. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy* 2008; **63**:47–57.
- 34 Tang YJ, Lee WJ, Chen YT *et al*. Serum testosterone level and related metabolic factors in men over 70 years old. *J Endocrinol Invest* 2007; **30**:451–8.
- 35 Folsom AR, Golden SH, Boland LL, Szklo M. Association of endogenous hormones with C-reactive protein, fibrinogen, and white blood count in post-menopausal women. *Eur J Epidemiol* 2005; **20**:1015–22.
- 36 Sorensen K, Aksglaede L, Munch-Andersen T *et al*. Sex hormone-binding globulin levels predict insulin sensitivity, disposition index, and cardiovascular risk during puberty. *Diabetes Care* 2009; **32**:909–14.