

Asthma severity is associated with body mass index and early menarche in women

Raphaëlle Varraso^{1*}, PhD student

Valérie Siroux^{1,2}, PhD

Jean Maccario¹, PhD

Isabelle Pin², MD

Francine Kauffmann¹, MD

on behalf of the Epidemiological study on the Genetics and Environment of Asthma (EGEA)

¹INSERM U472-IFR 69, Epidemiology and biostatistics, Villejuif, France

²Grenoble CHU, Grenoble, France

* Corresponding author:

Raphaëlle Varraso

INSERM U472

16 avenue Paul Vaillant Couturier, 94807 Villejuif cedex, France

Telephone (33) 1 45 59 52 61; Fax (33) 1 45 59 51 69

Email: varraso@vjf.inserm.fr

Running title: Body mass index and asthma severity

Subject category list: 57

Word count: 3176

ABSTRACT

Asthma severity in relation to body mass index (BMI) has rarely been studied. The relation between BMI and asthma severity was studied by sex in 366 adult asthmatics from the Epidemiological study on the Genetics and Environment of Asthma, (EGEA), a case control and family study on asthma. Factors related to asthma severity and BMI such as smoking, FEV₁, bronchial hyperresponsiveness (BHR) and dyspnea were taken into account. The influence of early menarche was studied to assess the potential role of hormonal factors. Clinical asthma severity in the last 12 months was assessed by a score (0-7), based on the frequency of asthma attacks, persisting symptoms between attacks and hospitalization. Asthma severity which was unrelated to gender, increased with BMI in women ($p=0.0001$), but not in men ($p=0.3$). In women, the association remained after adjustment on age, FEV₁, smoking habits, BMI-adjusted dyspnea and taking into account familial dependence ($p=0.0001$). The association between BMI and severity was stronger in women with early menarche than in women without early menarche (p interaction = 0.02). Findings support the hypothesis of hormonal factors involved in the severity of asthma.

Abstract word count: 185

Keywords: asthma severity, body mass index, gender, menarche.

INTRODUCTION

In the last decades a significant and a concomitant increase in the prevalence of both asthma and obesity occurred worldwide. Association of asthma incidence with body mass index (BMI) and weight gain has been reported in women (1-4) but not in men in most studies (2, 4), but not in all (5, 6, 7). Decrease in physical activity due to asthma does not seem to explain the association (2). It is well known that asthma incidence is greater in boys than in girls (8, 9). With the onset of puberty, asthma incidence and frequency of hospital admissions for asthma are higher among women compared with men and remain higher throughout the reproductive years (10). Gender differences may depend of hormonal factors (sex-related) as well as gender-related behaviors (11-13). Early onset of puberty and obesity independently favor the persistence of asthma (14).

Women have more severe asthma than men (15), report more dyspnea (8) and have more bronchial hyperresponsiveness (BHR) (16), associations only partly understood. Obesity may directly affect the asthma phenotype by mechanical effects including airways latching and increasing in airways resistance and responsiveness to methacholine (17). It is known that the perception of airflow limitation is different according to sex and it has been suggested that obesity could be more related to dyspnea than to airflow limitation (18). Therefore, sex-related patterns of asthma may depend on interrelationships of BMI, lung function, BHR and dyspnea. Factors related to asthma severity may be similar or different from those related to asthma incidence. Only one study reported an association of BMI with asthma severity in women, but not in men (19). Until now, no epidemiological study has included hormones levels (leptin and sexual hormones) to establish their role in sex-related patterns of asthma and related phenotypes. The cumulative frequency of ovulatory menstrual cycles is a critical determinant of a hormone-dependent disease, such as breast cancer (20), and results on breast

cancer provide a research frame regarding the role of hormone-related events for asthma.

The purpose of the study was to determine the relation between BMI and severity of asthma by sex, taking into account factors related to asthma severity and BMI such as smoking, FEV₁, BHR or dyspnea and to investigate the potential role of hormonal factors, by studying early menarche. Some of the results have been previously reported in the form of an abstract (21).

METHODS

The design of EGEA combines a case-control study and a family study of asthmatic cases. The protocol and descriptive characteristics have been described elsewhere (22-25, see online supplement). Out of the 368 subjects without missing data on BMI and FEV₁, 2 outliers with morbid obesity were excluded (see online data supplement). The analysis was performed on 366 adult (≥ 16 years) asthmatics (211 cases and 155 relatives of cases).

Subjects answered a questionnaire regarding respiratory symptoms, environment and treatment (including inhaled and oral steroids) based on international standardized questionnaires (25). For relatives, asthma status was based on a positive answer to either "Have you ever had attacks of breathlessness at rest with wheezing?" or "Have you ever had asthma attacks?". Dyspnea was evaluated according to 5-point grading scale. For all asthmatics, the severity was assessed based on international guidelines (26), similarly as in the study of the familial resemblance of asthma severity (27). Three criteria of severity were assessed (see Table E1): the clinical asthma severity score in the last 12 months, hospitalization for asthma during life and the use of inhaled steroids in the last 12 months. The clinical score was the primary outcome and was evaluated as a continuous variable. It varied between 0 and 7 and was based on frequency of asthma attacks (from 0 for less than once a month to 3 for at least once a day), persisting symptoms between attacks (from 0 for none to 3 for limiting activities) and hospitalization in the past 12 months (0 for none, 1 for more than 0).

A three-class BHR score was defined corresponding to the cumulative dose of methacholine producing a decline of 20% or more in FEV₁: none (dose > 4 mg), mild (0.25 mg < dose \leq 4 mg) and severe (dose \leq 0.25 mg). The analysis using BHR did not include 184

subjects corresponding to 77 with baseline FEV₁ ≤ 80%, 16 with post diluent decline, 16 contraindications, 3 refusals, 9 technical problems, and 63 for whom the test was not completed to 4 mg despite a decrease in FEV₁ less than 20%. Body mass index (weight/height²) was calculated and classified according to sex-specific quintiles. Analyses were also performed using BMI as a continuous variable and the hypothesis of a U or a J-shaped relation was tested using quadratic models (BMI²). Early menarche was defined by menarche at 11 years or earlier. Irregular cycles were defined by at least 5 days of difference between two cycles.

Univariate relationships between variables were explored using χ^2 tests, correlation and analysis of variance. Multivariate linear, logistic and ordinal logistic regressions were also performed. As there is no simple cause effect relationship between dyspnea and the clinical severity score, models have been run including residuals of dyspnea grades a priori adjusted on BMI in a linear regression model. All the analyses were stratified by sex. Familial dependence between observations was taken into account using the Generalized Estimated Equations (GEE) (Genmod and Mixed procedure in the statistical software SAS, (SAS Institute, Cary, NC, USA)).

(506 words)

RESULTS

Population characteristics

The subjects were in average 36.8 years old, and 42% of men and 60% of women were never smokers. About 20% of the women had early menarche (table 1) and 13% were menopausal. Age of menarche was negatively related with BMI ($r = -0.20$, $p = 0.009$). No relation was found between irregular cycles and age at menarche. The age at the time of the study was unrelated to early menarche ($m \pm SD$: 34.5 ± 13.7 vs. 35.4 ± 12.1 years, $p=0.7$, in women with and without early menarche respectively).

Relationship of BMI to potential confounders

FEV₁% predicted and BHR were unrelated to BMI. Women had more severe BHR than men, but it was on the borderline of significance ($p = 0.09$) (table 2), a relation similar after adjustment on age, BMI, smoking habits and FEV₁% predicted (OR: 1.71, 95% CI: 0.87 to 3.36, $p = 0.12$).

Dyspnea was positively and linearly related to BMI after adjustment on sex (OR: 1.20, 95% CI: 1.11 to 1.28), a relation not modified after further adjustment on age, smoking habits, FEV₁% predicted and BHR. Women reported significantly more dyspnea than men (OR: 2.24, 95% CI: 1.47 to 3.43) and in particular more severe dyspnea (grade ≥ 4 ; OR: 2.58, 95% CI: 1.32 to 5.02). Taking into account age, BMI, smoking habits, FEV₁% predicted and BHR even increased the strength of the association between dyspnea and sex (OR: 3.71, 95% CI: 1.79 to 7.68). In men as in women, dyspnea was strongly related with the asthma severity clinical score ($r = 0.28$, $p = 0.0006$ in men; $r = 0.44$, $p < 0.0001$ in women).

Univariate relationships with asthma severity

Asthma severity was unrelated to sex considering the clinical score, inhaled steroids or hospitalizations during life (table 2). Out of 81 asthmatics who reported any hospitalization during life, only 28 had one in the last twelve months. Women with early menarche had a more severe clinical score than the others (mean \pm SD: 2.00 ± 2.27 vs. 1.37 ± 1.51 respectively; $p = 0.06$). The clinical score was unrelated to age at menopause or irregular cycles.

Multivariate relationships with asthma severity

The clinical asthma severity score was related to BMI in women, but not in men (table 3). A borderline interaction was found between sex and body mass index on the clinical asthma severity score ($p=0.09$) but reached the significance level after adjustment on age, smoking habits, FEV₁% predicted and BMI-adjusted grade of dyspnea ($p=0.02$). The association between BMI and the clinical asthma severity score remained in women after taking into account age, smoking habits and FEV₁% predicted and no interaction was found between smoking habits and BMI on asthma severity in women. Further adjustment on BHR marginally decreased the association. To assess the relation of BMI on severity unrelated to dyspnea, a model has been run including dyspnea. Due to the strong correlation between BMI and dyspnea, the indicator of dyspnea included was BMI-adjusted dyspnea grade. After adjustment on BMI-adjusted dyspnea, BMI remained related to the clinical asthma severity score in women but not in men ($p=0.0001$, $p=0.7$, respectively). Taking into account familial dependence led to similar figures and ordinal logistic regression models confirmed these findings (see online data supplement). The exclusion of menopausal women and taking inhaled or per os steroids into account gave the same results. Other aspects of severity (treatment by inhaled steroids and hospitalization) were unrelated to BMI.

Role of early menarche

Early menarche modified the relation of BMI quintiles (figure 1) with clinical score (p interaction = 0.02). Adding the two obese women (1 without and 1 with early menarche) to those in the highest quintiles led to similar results, with a p for trend of borderline significance in women without early menarche (p = 0.09) and significant in women with early menarche (p = 0.007; p interaction = 0.11).

Results were confirmed by considering BMI as a continuous variable. Clinical severity score increased with the increase of BMI in women with early menarche (r = 0.49, p = 0.005) and in a much lesser extent in those without early menarche (r = 0.20, p = 0.03); p interaction = 0.03). Including BMI² in addition to BMI in the model even increased the interaction (p = 0.001).

DISCUSSION

In the 366 asthmatics from the EGEA study, the severity of asthma assessed by a clinical score increased with BMI in women but not in men. In women, the association remained after adjustment for confounders. Furthermore, the association between BMI and asthma severity was stronger in women with early menarche than in women without. Results support the role of hormonal factors in the severity of asthma.

Findings extend the observations of the relation between asthma and BMI, already found in children and adults (1-7, 14, 17, 28-30). In adults, the relationship has been consistently observed in women (1-4, 7, 17, 28). Whereas no association has been observed in men in most studies (2, 4, 17, 28), it remains unclear if there is any relationship between obesity and asthma in men. In children, positive associations have been reported between BMI and an increased risk of new-onset asthma (30). In adults, one study found a positive association between BMI and asthma in men from minority groups (7) and some have reported U-shaped associations (5, 6), a result consistent with the observed U-shaped association of BMI and BHR in men (31). The proportion of obese subjects as well as nutrition patterns were variable in previous studies (5, 6), with a survey from China with 95% of the subjects under 25 kg/m² (5) and one in United States with a high proportion of overweight and obese subjects (46.9% were over 25 kg/m²) (6). We did not observe an association of BMI with BHR, but the sample with the information was limited. Conflicting results have been observed regarding the association of BHR with BMI with U-shaped (31), a paradoxical association with decreased BHR with increased BMI in children (32), which disappeared after adjustment for FEV₁ level. Consistent with our observations no association of BMI with BHR, despite an association with high BMI with recent asthma was observed in a study on 1900 adults (33). A single study on 321 asthmatics already reported an association

of BMI with asthma severity, assessed by the dose of inhaled steroids and exacerbation in the last year (19). Women with severe asthma had a BMI greater by 1.6 kg/m² than those with controlled asthma, whereas no association was observed in men. No association of obesity with health care utilization was observed in 572 asthmatics admitted in emergency departments (34). In the EGEA study, no association between asthma severity and BMI was observed in men, even when testing a U-shape relation by considering models with a quadratic term.

Our study has several limitations. The small number of obese subjects to study obesity per se in the population precludes to provide a definite answer regarding obese subjects. The lack of information on the dose of inhaled steroids, does not allow to distinguish asthma severity from asthma control. Asthma clinical severity in the EGEA study has been standardized and already used to assess the role of various factors and to evidence its familial resemblance (27). Previously, we reported in the EGEA study that active smoking increased asthma severity (35). In the present analysis, smoking did not modify the association between BMI and severity in women. The definition of asthma severity in epidemiology is difficult, an aspect that we recently reviewed (36). To approach the new GINA guidelines, which include therapy, we have performed analyses adjusted for therapy and results are unchanged. Another limitation of the study is that few asthmatics had high severity scores, which limits the interpretation of the severity score, analyzed as a continuous variable. However, similar conclusions were obtained when using ordinal logistic regressions, which do not assume the hypothesis of linearity for the score. Finally, data should be interpreted with caution due to the cross-sectional nature of the study.

Dyspnea is a dimension of asthma severity and was strongly related to BMI. The basis of the 5-grade dyspnea scale is the magnitude of physical activity needed to cause

breathlessness (37). Taking into account residuals of grades of dyspnea adjusted on BMI instead of dyspnea, allowed to study the part of dyspnea not related to BMI, which may be some proxy for decreased physical activity. Our result is consistent with the hypothesis that the relation of asthma severity to obesity is not the reflect of a diminution of physical activity leading to weight gain, but studies with a more direct assessment of physical activity are warranted before concluding on that point. Longitudinal studies, which indicate that obesity took place before asthma (1, 2, 4), also support the hypothesis that the association of asthma (or asthma severity) with BMI is not mediated by a decrease in physical activity. Dyspnea is also a key component of quality of life, in particular in asthma-specific scales. Dyspnea among all other respiratory symptoms (cough, phlegm, wheezing and dyspnea) is the typical female symptom for reasons still not fully understood, likely not only through adiposity-related factors. Therefore the situation of dyspnea in female asthma severity may be different than dyspnea in male asthma severity. It is therefore of interest that the association of BMI with the severity score observed only in women remained after adjusted for this symptom. BHR, as dyspnea, is more prevalent in women than in men (16). Gender difference for dyspnea was not explained by BHR, result described for the first time. Further studies in men and women with BMI, quality of life scales and BHR are necessary to disentangle gender-specific factors of asthma severity.

Several arguments support the role of hormones in asthma and asthma severity in women. Decreased incidence at menopause (10), variation in visits to emergency departments according to menstrual cycle (38) have been reported, although the effects of menstrual cycles on asthma are not well understood (39) and there is limited evidence of the association of hormone levels with asthma-related traits (40, 41).

In general, limited information is available on the relation of hormone-related events with asthma, persistence or severity of asthma and asthma-related traits. In the EGEA study, it

has been shown that total IgE and atopy decreased with menopause, and that eosinophils were related to perimenstrual asthma and more strongly related to persistent asthma in women than in men (42). Increase in body silhouettes since menarche was evidenced as a strong factor of asthma incidence in a large prospective cohort study of women (3). The strong association of BMI with asthma severity in women with early menarche supports the hypothesis of the role of hormonal factors. It is unlikely that the effect relate to some recall bias as women who reported early menarche had the same age as the others, but the small number of women with early menarche and the cross-sectional nature of the study are limitations. It is well known that BMI is related to rapid sexual maturation, increases estrogens and leads to early menarche (43). In the longitudinal Tucson Children's Respiratory Study, obesity was shown to relate to the incidence of wheezing in girls with early menarche (29), and obesity and early onset of puberty to be independent risk factors for persistence of asthma after the onset of puberty in both boys and girls (14). Early menarche is a strong factor of breast cancer, an hormone-related disease (20). Earlier onset of regular menstrual cycles is associated to early regular ovulatory menstrual cycles, a risk factor for the disease. Two explanations have been proposed: first that it is related to a long duration of ovarian activity and second that it corresponds to a long –lasting effect of age at menarche on estrogen concentrations during adulthood (44). Estrogen and progesterone, at pregnancy levels, favor the development of a Th2 profile, a necessary condition for a successful pregnancy. Mechanisms involved may include inhibition of Th1 inflammatory response through modulation both of quantity (decreasing recruitment of the inflammatory cells) and quality by the establishment of a Th2 type, a feedback of the effect of estrogen on the function of antigen presenting cells (45) and a decrease of apoptosis of Th2 cells by progesterone (46). Limited information is available regarding the potential effect of physiological levels of hormones on Th1/Th2 balance.

Besides the role of estrogens, leptin could play a key related role. Among the

numerous proteins associated to obesity, leptin plays the central role. Leptin is a 146 amino acid protein, encoded by the obesity (*ob*) gene and member of the IL-6 family of cytokines (pro-inflammatory cytokines). Secreted by the adipocytes, circulating level of leptin correlate with the amount of body fat and BMI and is a permissive factor for the initiation of pubertal events in both boys and girls (47). The role of leptin in the association between BMI and asthma remained poorly understood. In a population-based study, FEV₁ was shown to decrease with increase in leptin levels in non obese subjects, which could reflect the pro-inflammatory role of leptin (48) but no information on asthma status was available in that study. Recently, leptin has been shown to be a predictive factor for asthma in prepubertal children, especially in boys (49). Studies on the relations of lung function, asthma and asthma severity with sexual hormones and leptin are warranted.

In summary, we found that severity of asthma increased with BMI only in women and that this relation was stronger among women with early menarche. These data suggest that factors of asthma severity are sex-dependent and that hormonal factors could be involved in the severity of asthma.

EGEA Cooperative group

Respiratory epidemiology INSERM U472, Villejuif: I. Annesi-Maesano, F. Kauffmann (coordinator), M.P. Oryszczyn; INSERM U408, Paris: M. Korobaeff, F. Neukirch.

Genetics INSERM EMI 00-06, Evry: F. Demenais; INSERM U535, Villejuif: M.H. Dizier; INSERM U393, Paris: J. Feingold; CNG, Evry: M. Lathrop.

Clinical centres Grenoble: I. Pin, C. Pison; Lyon: D. Ecochard (deceased), F. Gormand, Y. Pacheco; Marseille: D. Charpin, D. Vervloet; Montpellier: J. Bousquet; Paris Cochin: A. Lockhart, R. Matran (now in Lille); Paris Necker: E. Paty, P. Scheinmann; Paris Trousseau: A. Grimfeld.

Data management INSERM ex-U155: J. Hochez; INSERM U472: N. Le Moual.

REFERENCES

1. 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* 1999;159:2582-2588.
2. 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;164:2045-2050.
3. Romieu I, Avenel V, Leynaert B, Kauffmann F, Clavel-Chapelon F. Body mass index, change in body silhouette, and risk of asthma in the E3N cohort study. *Am J Epidemiol* 2003;158:165-174.
4. 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;155:191-197.
5. Celedon JC, Palmer LJ, Litonjua AA, Weiss ST, Wang B, Fang Z, et al. Body mass index and asthma in adults in families of subjects with asthma in Anqing, China. *Am J Respir Crit Care Med* 2001;164:1835-1840.
6. Luder E, Ehrlich RI, Lou WY, Melnik TA, Kattan M. Body mass index and the risk of asthma in adults. *Respir Med* 2004; 98:29-37.
7. Kim S, Camargo CA Jr. Sex-race differences in the relationship between obesity and asthma: the behavioral risk factor surveillance system, 2000. *Ann Epidemiol* 2003 ;13:666-73.
8. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life

- span. *Thorax* 1999;54:1119-1138.
9. De Marco R, Locatelli F, Sunyer J, Burney P. Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med* 2000;162:68-74.
 10. Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. *Am J Respir Crit Care Med* 1995;152:1183-1188.
 11. Redline S, Gold D. Challenges in interpreting gender differences in asthma. *Am J Respir Crit Care Med* 1994;150:1219-1221.
 12. Krieger N. Genders, sexes, and health: what are the connections--and why does it matter? *Int J Epidemiol* 2003;32:652-657.
 13. Kauffmann F, Becklake MR. Sex and gender. In: Respiratory epidemiology in Europe. Annesi-Maesano I, Viegi G, Gulsvik A eds. *Eur Respir Mon* 2000;14:288-304.
 14. Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at onset of puberty. *Am J Respir Crit Care Med* 2004 ;170:78-85
 15. Prescott E, Lange P, Vestbo J. Effect of gender on hospital admissions for asthma and prevalence of self-reported asthma: a prospective study based on a sample of the general population. Copenhagen City Heart Study Group. *Thorax* 1997;52:287-289.
 16. Leynaert B, Bousquet J, Henry C, Liard R, Neukirch F. Is bronchial hyperresponsiveness more frequent in women than in men? A population-based study. *Am J Respir Crit Care Med* 1997;156:1413-1420.

17. Tantisira KG, Weiss ST. Complex interactions in complex traits: obesity and asthma. *Thorax* 2001;56 (suppl 2):ii64-74.
18. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. *Arch Intern Med* 2002;162:1477-1481.
19. The ENFUMOSA study group. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Respir J* 2003;22:470-477.
20. Bernstein L, Ross RK. Endogenous hormones and breast cancer risk. *Epidemiol Rev* 1993;15:48-65.
21. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Body mass index, early menarche and severity of asthma in the EGEEA study. *Eur Respir J* 2004;24(suppl):21s-22s.
22. Kauffmann F, Dizier MH, Pin I, Paty E, Gormand F, Vervloet D, et al. Epidemiological study of the genetics and environment of asthma, bronchial hyperresponsiveness, and atopy: phenotype issues. *Am J Respir Crit Care Med* 1997;156:S123-S129.
23. Kauffmann F, Dizier MH, Annesi-Maesano I, Bousquet J, Charpin D, Demenais F, et al. Etude épidémiologique des facteurs génétiques et environnementaux de l'asthme, l'hyperréactivité bronchique et l'atopie (EGEEA) - Protocole et biais de sélection potentiels. *Rev Epidemiol Sante Publique* 2001;49:343-356.
24. Kauffmann F, Dizier MH, Annesi-Maesano I, Bousquet J, Charpin D, Demenais F, et al. EGEEA (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy)--descriptive characteristics. *Clin Exp Allergy* 1999;29 Suppl 4:17-21.
25. Kauffmann F, Annesi-Maesano I, Liard R, Paty E, Faraldo B, Neukirch F, et al.

Construction et validation d'un questionnaire en épidémiologie respiratoire. L'exemple du questionnaire de l'étude épidémiologique des facteurs génétiques et environnementaux de l'asthme, l'hyperréactivité bronchique et l'atopie (EGEA). *Rev Mal Respir* 2002;19:323-333.

26. Global initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop Report, February 2002. NIH publication no. 02-3659. 2002; NIH publication no.02-3659.
27. Pin I, Siroux V, Cans C, Kauffmann F, Maccario J, Pison C, et al. Familial resemblance of asthma severity in the EGEA study. *Am J Respir Crit Care Med* 2002;165:185-189.
28. Weiss ST, Shore S. Obesity and Asthma: directions for research. *Am J Respir Crit Care Med* 2004;169:963-968.
29. 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;163:1344-1349.
30. Gilliland FD, Berhane K, Islam T, McConnell R, Gauderman WJ, Gilliland SS, et al. Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol* 2003;158:406-415.
31. Litonjua AA, Sparrow D, Celedon JC, DeMolles D, Weiss ST. Association of body mass index with the development of methacholine airway hyperresponsiveness in men: the Normative Aging Study. *Thorax* 2002;57:581-585.
32. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL, Childhood Asthma Management Program Research Group. Association of body mass with pulmonary function in the

- childhood asthma management program (CAMP). *Thorax* 2003;58:1036-41.
33. Schachter LM, Salome CM, Peat JK, Woolcock AJ. Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness. *Thorax* 2001;56:4-8.
 34. Thomson CC, Clark S, Camargo CA Jr. Body mass index and asthma severity among adults presenting to the emergency department. *Chest* 2003;124:795-802.
 35. Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. *Eur Respir J* 2000;15:470-477.
 36. Siroux V, Pin I, Pison C, Kauffmann F. Asthme sévère en population générale : définitions et prévalence. [Severe asthma in general population: definitions and prevalence]. *Rev Mal Respir* 2004 (in press).
 37. Mahler DA, Jones PW eds. Key outcomes in COPD exacerbations and dyspnea. *Eur Respir Rev* 2002;12:1-54.
 38. Zimmerman JL, Woodruff PG, Clark S, Camargo CA. Relation between phase of menstrual cycle and emergency department visits for acute asthma. *Am J Respir Crit Care Med* 2000;162:512-515.
 39. Vrieze A, Postma DS, Kerstjens HA. Perimenstrual asthma: a syndrome without known cause or cure. *J Allergy Clin Immunol* 2003;112:271-282.
 40. Pauli BD, Reid RL, Munt PW, Wigle RD, Forkert L. Influence of the menstrual cycle on airway function in asthmatic and normal subjects. *Am Rev Respir Dis* 1989;140:358-362.
 41. Weinamn GG, Zacur H, Fish JE. Absence of changes in airway responsiveness during

- the menstrual cycle. *J Allergy Clin Immunol* 1987;79:634-638.
42. Siroux V, Curt F, Oryszczyn MP, Maccario J, Kauffmann F. Role of gender and hormone-related events on IgE, atopy and eosinophils in the EGEA study. *J Allergy Clin Immunol* 2004;114:491-498.
43. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of menarcheal age to obesity in childhood and adulthood: the Bogalusa heart study. *BMC Pediatr* 2003 Apr;3. Available from: URL: <http://www.biomedcentral.com/1471-2431/3/3>.
44. Apter D, Reinila M, Vihko R. Some endocrine characteristics of early menarche, a risk factor for breast cancer, are preserved into adulthood. *Int J Cancer* 1989;44:783-787.
45. Salem ML. Estrogen, a double-edged sword: modulation of TH1- and TH2-mediated inflammations by differential regulation of TH1/TH2 cytokine production. *Curr Drug Targets Inflamm Allergy* 2004;3:97-104.
46. Piccinni MP, Scaletti C, Maggi E, Romagnani S. Role of hormone-controlled Th1- and Th2 -type cytokines in successful pregnancy. *J Neuroimmunol* 2000;109:30-33.
47. Garcia-Mayor RV, Andrade A, Rios M, Lage M, Dieguez C, Casanueva FF. Serum leptin levels in normal children: relationship to age, gender, body mass index, pituitary-gonadal hormones, and pubertal stage. *J Clin Endocrinol Metab* 1997;82:2849-2855.
48. Sin DD, Man SFP. Impaired lung function and serum leptin in men and women with normal body weight: a population based study. *Thorax* 2003;58:695-698.
49. Guler N, Kurerleri E, Ones U, Tamay Z, Salmayenli N, Darendeliler F. Leptin: does it have any role in childhood asthma? *J Allergy Clin Immunol* 2004;114:254-259.

Figure 1. Relation between asthma clinical severity score and sex-specific quintiles of body mass index among asthmatic men and among women according to early menarche.

Table 1 Characteristics of the population

	Men (n=189)	Women (n=177)
Age, m \pm SD	38.7 \pm 14.1	35.6 \pm 12.6
(range)	(16.0 - 68.8)	(16.0 -65.9)
Body mass index*, m \pm SD	24.1 \pm 3.5	22.4 \pm 3.5
Smoking habits, n	185	176
Never smokers, %	42.1	60.2
Ex-smokers, %	35.7	20.5
<20 g/day, %	14.6	18.2
\geq 20 g/day, %	7.6	1.1
Hormonal factors, n		175
Age at menarche, m \pm SD	/	12.7 \pm 1.5
Early menarche (\leq 11 y), %	/	21.7
Menopausal women, n	/	20
Age at menopause, m \pm SD	/	48.0 \pm 6.2
Irregular cycles, %	/	7.7

* Sex-specific BMI quintiles of BMI correspond to cut-offs of 20.9, 22.8, 24.9, 27.3 kg/m² in men and of 19.7, 21.2, 22.6, 24.8 kg/m² in women.

Table 2 Dyspnea, severity of asthma, lung function and bronchial responsiveness in asthmatic men and women

	Men (n=189)	Women (n=177)
Dyspnea, n	183	173
Grade 1, %	56.8	37.0
Grade 2, %	26.2	35.9
Grade 3, %	8.2	8.1
Grade 4, %	4.4	9.8
Grade 5, %	4.4	9.2
Asthma severity criteria		
Clinical score (last 12 months), n, m \pm SD	156	149
	1.85 \pm 1.83	1.48 \pm 1.71
Inhaled steroids (last 12 months), n, %	188	176
	54.8	55.1
Hospitalization ever, n, %	189	177
	19.6	24.9
FEV ₁ % predicted, m \pm SD	91.2 \pm 20.8	95.5 \pm 20.2
FEV ₁ \leq 80% predicted, %	27.5	18.1
Bronchial responsiveness, n	92	90
No BHR (PD ₂₀ > 4 mg), %	29.4	22.2
Mild BHR (PD ₂₀ \leq 4 mg and > 0.25 mg), %	32.6	28.9
Severe BHR (PD ₂₀ \leq 0.25 mg), %	38.0	48.9

Table 3 Relations between asthma clinical severity score and body mass index according to sex

	$\beta \pm SD^*$	p	p interaction†
Men			
Unadjusted (n =156)	0.053 \pm 0.042	0.3	
Adjusted on age, smoking habits and FEV ₁ % predicted (n = 153)	0.018 \pm 0.045	0.7	
Adjusted on age, smoking habits, FEV ₁ % predicted and BHR (n = 72)	0.043 \pm 0.068	0.5	
Adjusted on age, smoking habits, FEV ₁ % predicted and residual of grade of dyspnea‡ (n=148)	0.017 \pm 0.044	0.7	
Women			
Unadjusted (n =149)	0.156 \pm 0.039	0.0001	0.09
Adjusted on age, smoking habits and FEV ₁ % predicted (n = 148)	0.162 \pm 0.040	0.0001	0.03
Adjusted on age, smoking habits, FEV ₁ % predicted and BHR (n=74)	0.149 \pm 0.056	0.01	0.16
Adjusted on age, smoking habits, FEV ₁ % predicted and residual of grade of dyspnea‡ (n=145)	0.183 \pm 0.038	0.0001	0.02

Severity score as a continuous variable (0-7) was the dependent variable in all linear regression models. BMI was expressed in kg/m². Other continuous variables included in models were age (years), FEV₁% predicted and dyspnea. Categorical variables included were smoking habits (never smokers, ex-smokers, current smokers), bronchial hyperresponsiveness (BHR 3 class, see methods).

* β represents the variation in the severity score for an increased of 1 kg/m² for BMI. The last model for women shows for example that for an increase of 5 kg/m² in BMI, the severity score increased by 5 x 0.183=0.91.

† interaction between sex and body mass index on the clinical asthma severity score.

Table 3 (cont'd)

‡ grade of dyspnea included in that model was the residual of dyspnea after adjustment on BMI through sex-specific linear regression models.

Taking into account familial dependence led to similar figures.

Ordinal logistic regression models confirmed these findings (see online data supplement).

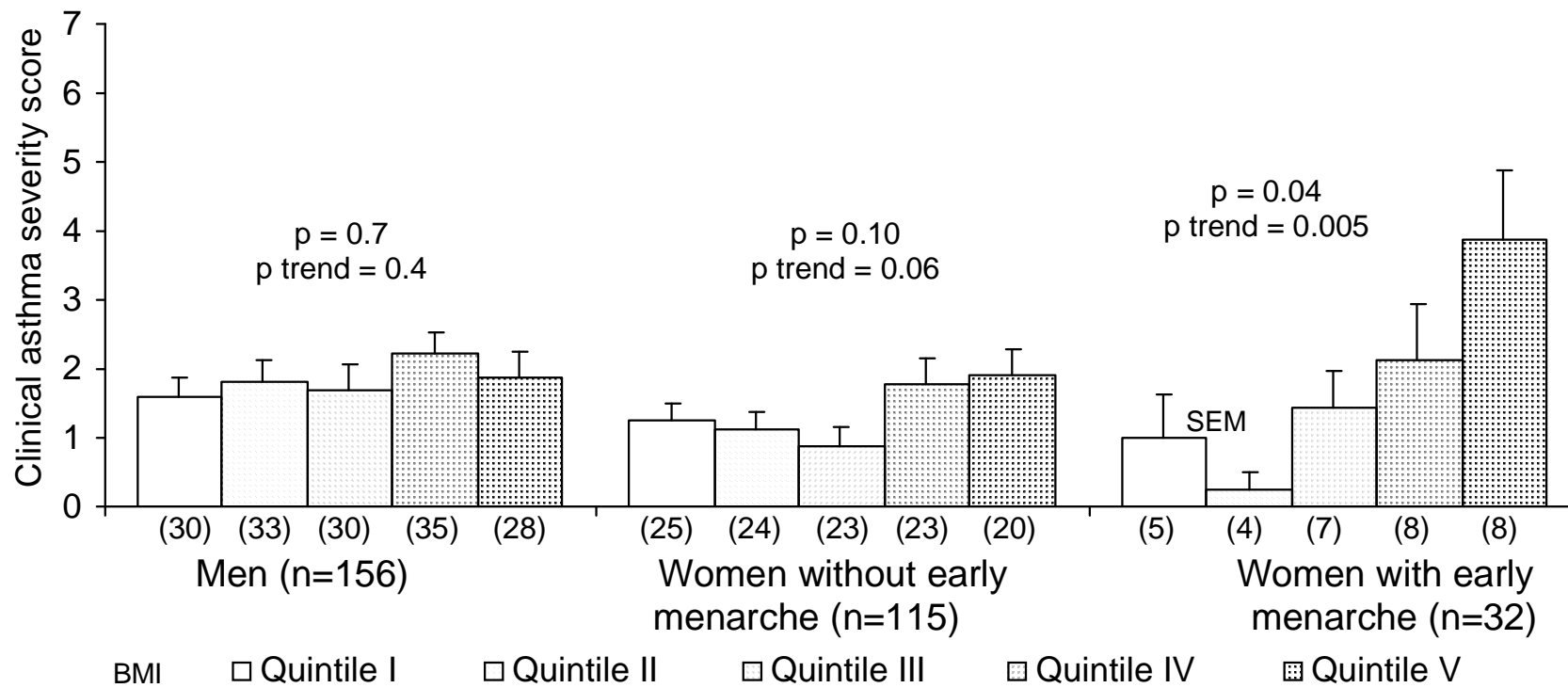


Figure 1.