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

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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, FEV$_1$, 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 ≤ 4 mg) and severe (dose ≤ 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 χ² 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 ± 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 ± 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, FEV$_1$% 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 FEV$_1$% 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 BMI$^2$ 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


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

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

* 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

<table>
<thead>
<tr>
<th></th>
<th>Men (n=189)</th>
<th>Women (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea, n</td>
<td>183</td>
<td>173</td>
</tr>
<tr>
<td>Grade 1, %</td>
<td>56.8</td>
<td>37.0</td>
</tr>
<tr>
<td>Grade 2, %</td>
<td>26.2</td>
<td>35.9</td>
</tr>
<tr>
<td>Grade 3, %</td>
<td>8.2</td>
<td>8.1</td>
</tr>
<tr>
<td>Grade 4, %</td>
<td>4.4</td>
<td>9.8</td>
</tr>
<tr>
<td>Grade 5, %</td>
<td>4.4</td>
<td>9.2</td>
</tr>
<tr>
<td>Asthma severity criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical score (last 12 months), n, m ± SD</td>
<td>156</td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>1.85 ± 1.83</td>
<td>1.48 ± 1.71</td>
</tr>
<tr>
<td>Inhaled steroids (last 12 months), n, %</td>
<td>188</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>54.8</td>
<td>55.1</td>
</tr>
<tr>
<td>Hospitalization ever, n, %</td>
<td>189</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td>19.6</td>
<td>24.9</td>
</tr>
<tr>
<td>FEV₁ % predicted, m ± SD</td>
<td>91.2 ± 20.8</td>
<td>95.5 ± 20.2</td>
</tr>
<tr>
<td>FEV₁ ≤ 80% predicted, %</td>
<td>27.5</td>
<td>18.1</td>
</tr>
<tr>
<td>Bronchial responsiveness, n</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>No BHR (PD20 &gt; 4 mg), %</td>
<td>29.4</td>
<td>22.2</td>
</tr>
<tr>
<td>Mild BHR (PD20 ≤ 4 mg and &gt; 0.25 mg), %</td>
<td>32.6</td>
<td>28.9</td>
</tr>
<tr>
<td>Severe BHR (PD20 ≤ 0.25 mg), %</td>
<td>38.0</td>
<td>48.9</td>
</tr>
</tbody>
</table>
Table 3 Relations between asthma clinical severity score and body mass index according to sex

<table>
<thead>
<tr>
<th></th>
<th>β ± SD*</th>
<th>p</th>
<th>p interaction†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (n = 156)</td>
<td>0.053 ± 0.042</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Adjusted on age, smoking habits and FEV₁% predicted (n = 153)</td>
<td>0.018 ± 0.045</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Adjusted on age, smoking habits, FEV₁% predicted and BHR (n = 72)</td>
<td>0.043 ± 0.068</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Adjusted on age, smoking habits, FEV₁% predicted and residual of grade of dyspnea; (n = 148)</td>
<td>0.017 ± 0.044</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (n = 149)</td>
<td>0.156 ± 0.039</td>
<td>0.0001</td>
<td>0.09</td>
</tr>
<tr>
<td>Adjusted on age, smoking habits and FEV₁% predicted (n = 148)</td>
<td>0.162 ± 0.040</td>
<td>0.0001</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted on age, smoking habits, FEV₁% predicted and BHR (n = 74)</td>
<td>0.149 ± 0.056</td>
<td>0.01</td>
<td>0.16</td>
</tr>
<tr>
<td>Adjusted on age, smoking habits, FEV₁% predicted and residual of grade of dyspnea; (n = 145)</td>
<td>0.183 ± 0.038</td>
<td>0.0001</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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.