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

Raphaëlle Varraso, Valérie Siroux, Jean Maccario, Isabelle Pin, Francine Kauffmann

Online data supplement

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Raphaëlle Varraso

Valérie Siroux

Jean Maccario

Isabelle Pin

Francine Kauffmann

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

METHODS

The general aim of the French cooperative Epidemiologic Study of the Genetics and Environment of Asthma (EGEA) (1991-1995) is to investigate the genetic and environmental factors of asthma, bronchial hyperresponsiveness (BHR), and atopy, taking the heterogeneity of the three traits into account (E01).

The design combines a case-control study and a family study. Patients with asthma (7 to 65 years of age), ascertained from chest clinics of six clinical centers in 5 French cities (Paris, Lyon, Marseille, Montpellier, and Grenoble) and their first-degree relatives and spouses were examined with a standard protocol, mostly based on international standardized tools. Control subjects (population and hospital-based) matched for age, month of examination and city, were evaluated with the same protocol. The study population included 348 asthmatics and their family members and 416 control subjects, in total 1847 subjects.

Asthmatic probands were defined by a positive answer to four questions (or to two or three questions after examination of their medical record) based on self-completed questionnaire (E02).

Q21. Have you ever had attacks of breathlessness at rest with wheezing?

Q22. Have you ever had asthma attacks?

If yes:

Q22a. Was this diagnosis confirmed by a physician?

Q22b. Have you had an asthma attack in the last 12 months?

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?". Subjects answered in a face to face interview to a detailed questionnaire on upper and lower airway symptoms, allergic symptoms, medical history, and environmental factors, using

British Medical Research Council/European Coal and Steel Community, American Thoracic Society, and European Community Respiratory Health Survey (ECRHS) questionnaires with additional questions when needed. The whole questionnaire is directly accessible through internet (E03). Dyspnoea was evaluated according to 5-point grading scale.

The choice of items used to assess asthma severity was based on international guidelines (E05), on their availability in the study, and on their applicability to the whole population of children and adults with asthma of the study. It allowed investigation of three dimensions of severity, similarly as in the study of the familial resemblance of asthma severity already performed (E06):

1. A clinical composite score ranging from 0 to 7 based on frequency of asthma attacks, persisting symptoms between attacks and hospitalization for asthma in the last 12 months (table E1).
2. The report of inhaled steroid use in the past 12 months (yes/no).
3. The hospitalization for asthma at any time in life.

For subjects with FEV_1> 80% predicted, a methacholine bronchial challenge test was performed (maximum dose, 4 mg). For others, a bronchodilator test was performed. Skin prick tests to 11 allergens, total immunoglobulin E (IgE) levels, Phadiatop test, leukocyte count, and standard differential count were performed. Bronchial testing and allergen skin-prick tests were performed according to the European Respiratory Health Survey protocol. A three-class BHR score was defined corresponding to the cumulative dose of methacholine producing a decline of 20% or more in FEV_1: none (decline < 20% at 4 mg), mild (0.25 mg < dose ≤ 4 mg) and severe (dose ≤ 0.25 mg). There were 368 subjects without missing data for BMI and FEV_1. After the exclusion of 2 outliers with morbid obesity described below, the analysis has been conducted on 366 adult asthmatics (≥ 16 years) corresponding to 211 cases and 155 asthmatic relatives of cases. The analysis using BHR does not include 184 subjects

corresponding to 77 with $FEV_1 \leq 80\%$, 16 with post diluent decline, 16 contraindications (myocardial infarction (1), use of medications for heart (7), use of medications for epilepsy (1), use of beta blockers (1), prostate problems (4), pregnancy (2)), 3 refusals, 9 technical problems, and 63 for whom the test was not completed to 4 mg despite a decrease in FEV_1 less than 20%). Missing data regarding the clinical severity score (61) were unrelated to sex, age, smoking habits, BMI, hormonal factors but was significantly associated to less asthma severity regarding the two other criteria based on inhaled steroids and hospitalization during life.

Body mass index (weight/height^2) was calculated and classified according to sex-specific quintiles. Cut off points for quintiles of BMI were 20.9, 22.8, 24.9 and 27.3 kg/m^2 in men and 19.7, 21.2, 22.6 and 24.8 kg/m² among women. 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 (BMI^2). 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.

Two women with morbid obesity were excluded from the analysis. The first outlier, ascertained as a proband was 39 years of age, 1.47 m, 95 kg (BMI = 46 kg/m^2), with menarche at 10 years, no history of diabetes and classified with a severity score of 1 (see below, figure E2), based on one hospitalization in the last 12 months, less than one attack of asthma per month and no symptoms between attacks in the last 12 months. She had her first asthma attack at 30 years, without attack between 36 and 38 years. She was non atopic, with IgE=82 IU/ml, 8470 leucocytes/mm^3, eosinophils 0% and FEV_1 % predicted equal to 74. She reported no cough, no phlegm, a dyspnea of grade 3, nocturnal symptoms (frequency unknown), use of beta 2 agonists, use of cromones and use of inhaled and oral steroids (unknown doses). She was hospitalized 6 times for asthma during her life, the first one when she was 35 years of age, with one emergency hospitalization at 35 years and one

hospitalization in intensive care unit at 37 years. The detailed data available for that woman suggest that she has not a mild asthma according to GINA guidelines and likely some form of brittle asthma. The second outlier was included as the mother of a pediatric case. She was 47 years old, 1.61m, 120 kg (BMI = 44 kg/m^2), with menarche at 15 years, a history of diabetes and hypertension. She has her first asthma attack at 2 years with a remission of attacks until 46 years. Her severity score was 3 (more than 1 attack of asthma / day without symptoms between attacks), had no current treatment for asthma except antihistaminics and was an ex-smoker with occupational exposure to textile dust.

Univariate relationships between variables were explored using $\chi 2$ tests, correlation and analysis of variance. Multivariate linear, logistic and ordinal logistic regressions were also performed. To performed ordinal logistic regressions, subjects in classes 4 to 7 were grouped in one group due to the small number of subjects. 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)). GEE were used only for continuous outcomes. In this case the main difference with standard GLM procedure is taking into account correlations within family members.

RESULTS

The graph of the distribution of the asthma clinical severity score is presented in figure E1. 36.1% of the subjects had an asthma clinical severity score equal to 0 and 15.4% of the subjects had an asthma clinical severity score greater or equal to 4.

The distribution of BMI according to the clinical asthma severity score among men and women according to early menarche with all subjects, including outliers is presented in figure E2.

Analyses conducted on tertiles instead of quintiles (see paper) led to the same conclusions. Cut off points for tertiles of BMI were 22.1 and 25.5 kg/m² in men and 20.7 and 23.4 kg/m² in women. The clinical asthma severity score was unrelated to tertiles of BMI in men (p=0.2, p trend=0.3), whereas the clinical score increased with tertiles of BMI in women (p=0.01, p trend=0.006). Early menarche modified the relation between the clinical score and tertiles of BMI. No association was found in women without early menarche (p=0.5, p trend=0.2), whereas a significant and a positive association was found in women with early menarche (p=0.008, p trend=0.004).

Analyses conducted using ordinal logistic regressions instead of linear regressions led to similar results (table E2). Whereas p values for the relation between asthma severity and BMI were 0.3 in men and 0.0001 in women considering severity as a continuous variable, they were 0.3 in men and 0.001 in women in an ordinal logistic regression. In models adjusted for age, smoking habits, FEV_1% predicted and residuals of grades of dyspnea adjusted for BMI, p values were 0.7 in men and 0.0001 in women for the linear regression models and 0.7 in men and 0.0001 in women for the ordinal logistic regression.

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Table E1 The clinical asthma severity score.

	Value
Frequency of asthma attacks in the past 12 months	
< 1 / month	0
≥ 1 / month and < 1 / week	1
≥ 1 / week and < 1 / day	2
≥ 1 / day	3
Persisting symptoms between attacks in the past 12 months	
None	0
Wheezing	1
Wheezing and shortness of breath	2
Activities limited by shortness of breath	3
Hospitalization for asthma in the past 12 months	
No	0
Yes	1
Clinical asthma severity score	0-7

Table E2 Relations between asthma clinical severity score and body mass index according to sex with linear and ordinal logistic regressions.

	Linear regression		Ordinal logistic regression	
	β ± SD*	p	OR (95% CI)†	p
Men				
Unadjusted (n =156)	0.053 ± 0.042	0.3	1.04 (0.96-1.13)	0.3
Adjusted on age, smoking habits, FEV_1% predicted and residual of grade of dyspnea‡ (n=148)	0.017 ± 0.044	0.7	0.99 (0.90-1.08)	0.7
Women				
Unadjusted (n =149)	0.156 ± 0.039	0.0001	1.15 (1.06-1.26)	0.001
Adjusted on age, smoking habits, FEV_1% predicted and residual of grade of dyspnea‡ (n=145)	0.183 ± 0.038	0.0001	1.22 (1.11-1.34)	0.0001

Severity score as a continuous variable (0-7) was the dependent variable in all linear regression models. Severity score as a qualitative variable (0-4) was the dependent variable in all ordinal logistic regression models (subjects in classes 4 to 7 were grouped in one group due to the small number of subjects).

BMI was expressed in kg/m^2. Other continuous variables included in models were age (years), FEV_1% 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/m^2 for BMI. The last model for women shows for example that for an increase of 5 kg/m^2 in BMI, the severity score increased by 5 x 0.183=0.91.

† The last model for women shows for example that a woman with a BMI of 25 kg/m^2 was around three times more at risk (1.22^5=2.7) of having a higher severity score than a woman with a BMI of 20 kg/m^2.

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

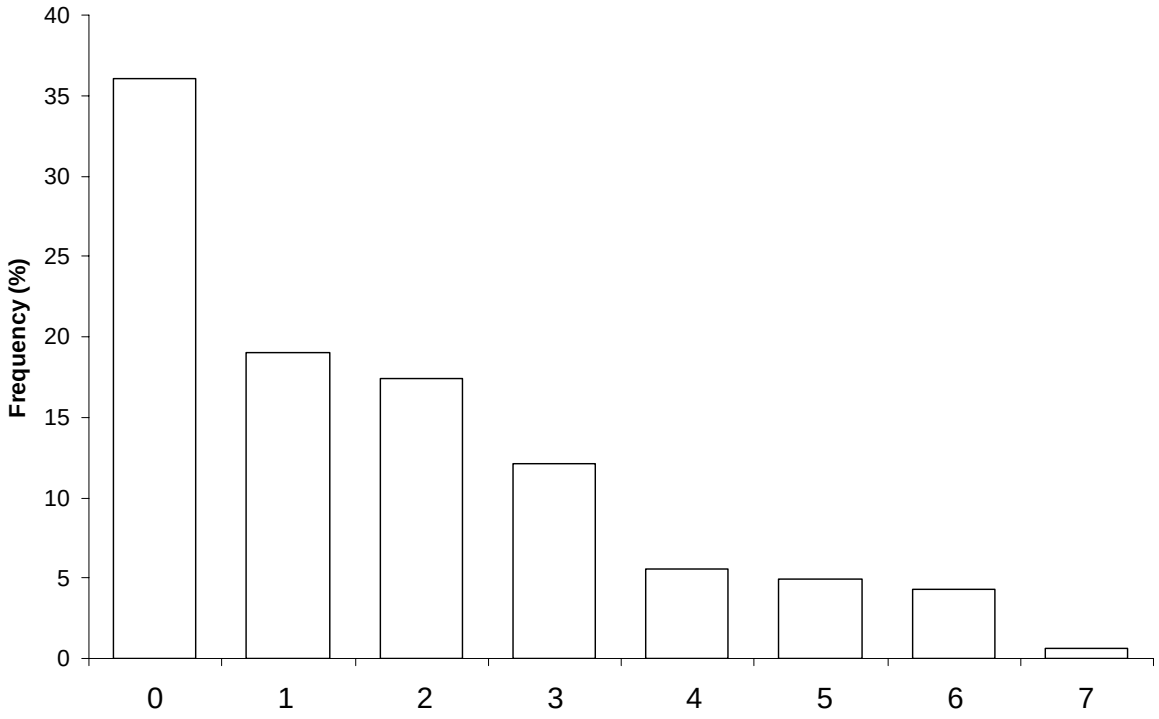

Figure E1 Distribution of the clinical asthma severity score (n=305).

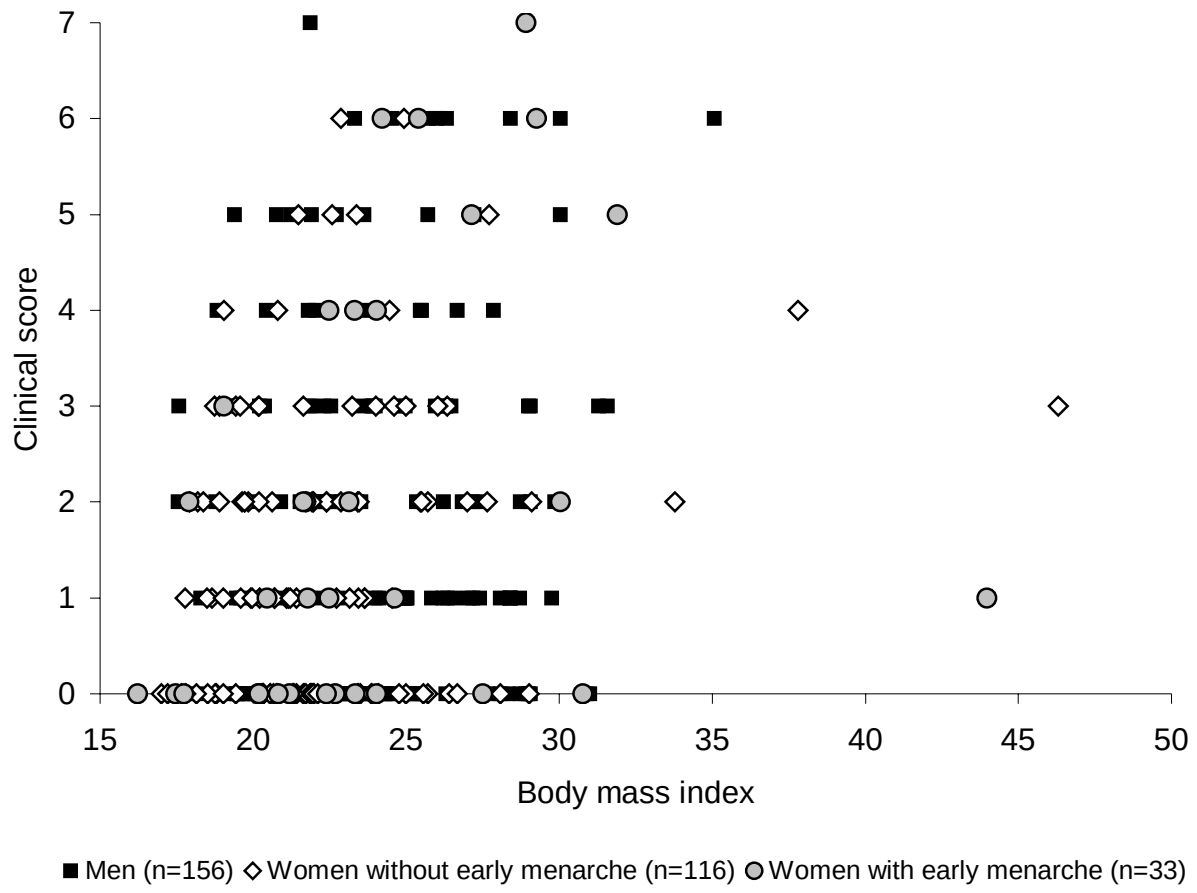

Figure E2 Distribution of body mass index according to the clinical asthma severity score among men and women according to early menarche.