

Body mass index, weight gain, and other determinants of lung function decline in adult asthma

Alessandro Marcon, MSc,^a Angelo Corsico, MD, PhD,^b Lucia Cazzoletti, MSc,^a Massimiliano Bugiani, MD,^c Simone Accordini, MSc,^a Enrique Almar, MD,^d Isa Cerveri, MD,^b David Gislason, MD,^e Amund Gulsvik, MD, PhD,^f Christer Janson, MD,^g Deborah Jarvis, MD,^h Jesús Martínez-Moratalla, MD,ⁱ Isabelle Pin, MD,^j Roberto de Marco, PhD,^a and the Therapy and Health Economics Group of the European Community Respiratory Health Survey Verona, Pavia, and Turin, Italy, Albacete, Spain, Reykjavik, Iceland, Bergen, Norway, Uppsala, Sweden, London, United Kingdom, and Grenoble, France

Background: Little is known about factors associated with lung function decline in asthma.

Objective: To identify the determinants of FEV₁ decline in adults with asthma with and without airflow obstruction at baseline.

Methods: An international cohort of 638 subjects with asthma (20-44 years old) was identified in the European Community Respiratory Health Survey (1991-1993) and followed up from 1998 to 2002. Spirometry was performed on both occasions. FEV₁ decline was related to potential determinants evaluated at baseline and during the follow-up by random intercept linear regression models. The analyses were stratified by the presence of airflow obstruction (FEV₁/forced vital capacity < 0.70) at baseline.

Results: In the group of individuals without airflow obstruction (n = 544), a faster FEV₁ decline was observed for subjects with intermediate body mass index (BMI) than for lean and obese subjects. FEV₁ decline was associated with weight gain independently of baseline BMI, and this association was stronger in men (20; 95% CI, 10-30, mL/y/kg gained) than in women (6; 95% CI, 1-11, mL/y). In the group of individuals with

airflow obstruction (n = 94), the absence of allergen sensitization and a low BMI at baseline were associated with a faster FEV₁ decline, whereas weight gain was not associated with decline.

Conclusions: The detrimental effect of weight gain on FEV₁ decline is particularly relevant in subjects with asthma who still do not have an established airflow obstruction. Our findings support the importance of weight management in asthma and recommend weight loss in overweight or obese individuals with asthma. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, lung function decline, airflow obstruction, body mass index, weight gain, obesity, FEV₁, allergen sensitization, prospective cohort study, predictors

Impaired pulmonary function, as measured by a low FEV₁, is a predictor of mortality in the general¹ as well as in the asthmatic population.² Subjects with asthma have a faster FEV₁ decline than subjects without asthma,³ and FEV₁ decline leads to persistent airflow obstruction for some individuals with asthma. Compared with subjects without obstruction, subjects with airflow obstruction have a more severe form of asthma, they may be on an inadequate asthma treatment, and their airways may already have been remodeled by chronic inflammation.⁴ Subjects in the 2 groups may have different individual characteristics and past exposures, a different history of asthma, and different determinants of lung function change over time. Some recent articles have suggested that long-term treatment with inhaled steroids may slow down the decline in FEV₁,⁵⁻⁷ particularly in subjects with elevated total IgE levels.⁷ However, little is known about other factors associated with rapid FEV₁ decline in adult asthma. We aimed at investigating the determinants of FEV₁ decline in a large, international, population-based cohort of subjects with asthma with or without airflow obstruction at baseline, who were followed up for 9 years in the European Community Respiratory Health Survey (ECRHS).

METHODS

Study design

The ECRHS is an international multicentre study of asthma. The first survey (ECRHS I)⁸ was carried out from 1991 to 1993 on random community-based samples of adults age 20 to 44 years. Each participant was sent a brief questionnaire (stage 1), and from those who responded, a 20% random sample was invited to undergo a more detailed clinical examination (stage 2). In addition, a sample (called "symptomatic sample" in the article) consisting of

From ^athe Unit of Epidemiology and Medical Statistics, Department of Medicine and Public Health, University of Verona; ^bthe Division of Respiratory Diseases, Fondazione "Istituto di Ricovero e Cura a Carattere Scientifico San Matteo Hospital" University of Pavia; ^cthe Unit of Pneumology, Consorzio Provinciale Antitubercolare, Azienda Sanitaria Locale 4 Torino 2 Piemonte, Turin; ^dthe Unit of Epidemiology, Department of Public Health, Junta de Comunidades de Castilla La Mancha, Albacete; ^ethe Department of Allergy, Respiratory Medicine and Sleep, Landspítali University Hospital, Reykjavik; ^fthe Department of Thoracic Medicine, Haukeland University Hospital, University of Bergen; ^gthe Department of Medical Sciences, Respiratory Medicine and Allergology, Uppsala University; ^hthe Respiratory Epidemiology and Public Health Group, National Heart and Lung Institute, Imperial College, London; ⁱServicio de Neumología, Hospital General Universitario de Albacete; and ^jPediatrics, Centre Hospitalier Universitaire de Grenoble and Institut National de la Santé et de la Recherche Médicale U823, Institut Albert Bonniot, Grenoble.

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Reprint requests: Alessandro Marcon, MSc, Unit of Epidemiology and Medical Statistics, Department of Medicine and Public Health, University of Verona, c/o Istituti Biologici II, Strada Le Grazie 8, 37134 Verona, Italy. E-mail: alessandro.marcon@univr.it.

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Abbreviations used

ATS: American Thoracic Society
 BMI: Body mass index
 ECRHS: European Community Respiratory Health Survey
 ETS: Environmental tobacco smoke
 FVC: Forced vital capacity
 Q₁: 1st quartile
 Q₃: 3rd quartile

subjects not already included in the random sample who reported asthmatic symptoms in the last 12 months, or who were using asthma medication in stage 1, was also studied. Subjects from the random and from the symptomatic samples were examined at the same time and with the same methods and accuracy. The ECRHS II⁹ was a follow-up study of all the participants in stage 2 of the ECRHS I, performed between 1999 and 2002 (the full protocol can be found at <http://www.ecrhs.org>). In both studies, subjects answered a standardized questionnaire administered by trained interviewers and they underwent lung function and blood tests. The current study includes data from 26 centers that took part in the ECRHS II. Ethical approval was obtained for each center from the appropriate institutional or regional ethics committee, and written consent was obtained from each participant.

Subjects and definitions

All individuals with current asthma identified in the ECRHS I (1991-1993) who had performed spirometry complying with the American Thoracic Society (ATS) criteria for reproducibility¹⁰ and who had participated in the ECRHS II were eligible for these analyses. Current asthma was defined as having reported, in the ECRHS I, asthma confirmed by a doctor, and having had asthmatic symptoms (wheeze; nocturnal chest tightness; attacks of breathlessness after activity, at rest, or at night time; asthma attacks), and/or having used inhaled/oral medicines because of breathing problems during the last 12 months. In the ECRHS I, 1348 subjects with current asthma had their lung function measured according to the ATS criteria. Compared with subjects from the symptomatic sample ($n = 648$), subjects from the random sample ($n = 700$) had a longer duration of the disease (median, 17 vs 15 years; $P < .01$), had a lower body mass index (BMI; 23 vs 24 kg/m²; $P < .01$) and included a smaller percentage of individuals with a low educational level (9% vs 15%; $P < .01$). Of these 1348 individuals, 860 (64%) participated in the second study (1999-2002) and were therefore eligible for the analyses. In the ECRHS II (1999-2002), some eligible subjects did not repeat spirometry (135 subjects), or their lung function was not measured in compliance with the ATS criteria (32 subjects), or they had used inhaled long-acting β_2 -agonists in the 12 hours before the test (26 patients), and were therefore excluded from the analyses.

Lung function

The maximum FEV₁ and forced vital capacity (FVC) of at least 2 and as many as 5 technically acceptable maneuvers were recorded, according to the ATS criteria for reproducibility.¹⁰ FEV₁ % predicted and FVC % predicted were calculated on the basis of the equations by Quanjer et al.¹¹ The average decline in FEV₁ (or FVC) during the follow-up was computed as the difference between FEV₁ (or FVC) measured in the ECRHS I and II, divided by the duration of the follow-up (expressed in mL/y). %FEV₁/FVC decline was also computed as the difference between %FEV₁/FVC in the ECRHS I and II, divided by the duration of the follow-up (expressed in %/y). Baseline airflow obstruction was defined as FEV₁/FVC < 0.70¹² at the first visit (ECRHS I). Because a bronchodilator challenge test was not part of the ECRHS core protocol, the follow-up spirometry was used to confirm baseline airflow obstruction. Accordingly, 29 subjects with baseline airflow obstruction, who had FEV₁/FVC ≥ 0.70 at the follow-up, were excluded from the analyses to reduce the number of false-positive individuals.¹³ A sensitivity analysis was performed to confirm that this did not affect our results (data not shown).

Clinical and questionnaire data

The clinical interview included questions on asthma and respiratory symptoms, smoking habits (smoking status, number of cigarettes smoked per day, age when subjects started smoking, age when they gave it up if they did), environmental tobacco smoke (ETS; ie, regular exposure to other people's smoke for 1 h/d or more), educational level (low if a subject had completed full-time education before the age of 16 years), age at first asthma attack, family asthma (mother/father ever had asthma), and use of inhaled steroids during the follow-up. Pack-years smoked were calculated for the period before the ECRHS I and for the follow-up period.¹⁴ Asthma duration was estimated as the difference between the age of the subject at the ECRHS I interview and the age when the first asthma attack occurred. The subject's weight (kg) and height (m) were measured, and BMI was calculated (weight/height²). BMI gain (kg/[m²·y]) or weight gain (kg/y) during the follow-up was computed as the difference between BMI/weight, measured in the ECRHS II and I, divided by the duration of the follow-up.

At baseline (ECRHS I), total IgE and specific IgE against house dust mite, cat dander, timothy grass, *Cladosporium* species, and a local allergen were measured. A subject was considered sensitized to any allergen if the assay result for at least 1 allergen was higher than 0.35 kU/L. Subjects performed a methacholine challenge test,¹⁵ but bronchial hyperresponsiveness was not considered in the analyses because about 20% of the subjects had not performed the challenge test, and the exclusion criteria for the test were associated with baseline FEV₁ (eg, FEV₁ < 70% predicted; FEV₁ < 1.5 L).

Statistics

Overall, 638 subjects were included in the analyses. All the analyses were stratified by the presence of airflow obstruction (FEV₁/FVC < 0.70) at baseline. Data were summarized as percentages, or medians with interquartile ranges (1st quartile-3rd quartile [Q₁-Q₃]). The χ^2 test, the Fisher exact test, and the Wilcoxon test were used to test differences, where appropriate ($\alpha = 0.05$). To assess the association between FEV₁ decline and the potential determinants, 2-level (with level-1 units, subjects, nested into level-2 units, centers, crossed by type of sample: random/symptomatic) random intercept multiple linear regression models¹⁶ were fitted to the data. The independent variables included in the models were BMI, educational level, pack-years, ETS exposure, sensitization to allergens, asthma duration, and family asthma measured at baseline; and BMI/weight gain, pack-years, and change in ETS exposure measured during the follow-up. The models were also adjusted for sex, age, height, and the interaction between inhaled steroid use during the follow-up (<4 years vs ≥ 4 years) and baseline total IgE (≤ 100 kU/L vs >100 kU/L).⁷ In the group of subjects without airflow obstruction, BMI squared was also included in the model, because it significantly ($P = .0009$) improved the model fitting. Statistical interactions were evaluated through likelihood ratio tests. The statistical analyses were performed using STATA software, release 9.2 (Stata Corp, College Station, Tex).

RESULTS**Comparison between included and excluded subjects**

Subjects excluded from the analyses ($n = 710$) were younger (median age [Q₁-Q₃], 32 [26, 38] years vs 34 [28, 40] years; $P < .001$), and they were more likely to be current smokers (38% vs 30%; $P = .01$) than subjects who were included ($n = 638$). However, the 2 groups were similar in regard to all the other baseline covariates (including BMI: median, 23 kg/m² in both groups), as well as baseline FEV₁ and FVC.

Characteristics and lung function of the subjects included in the analyses

Subjects in the random ($n = 299$) and subjects in the symptomatic ($n = 339$) samples were similar for baseline FEV₁

TABLE I. Baseline and follow-up characteristics of the subjects with asthma, stratified by the presence of airflow obstruction at baseline

	Airflow obstruction at baseline		P value
	No	Yes	
No. of subjects (%)	544 (85)	94 (15)	—
Sex (% female)	59	34	<.001
Baseline covariates			
Age (y)	33 (28-40)	36 (30-43)	.004
BMI (kg/m ²)	23 (21-26)	23 (21-26)	.57
Low educational level (%)	11	14	.50
Smoking habits			
Nonsmokers (%)	49	40	.25
Ex-smokers (%)	21	26	
Current smokers (%)	30	34	
Pack-years	0 (0-9)	2 (0-10)	.16
ETS (%)	48	44	.45
Sensitization to any allergen (%)	67	75	.12
Duration of asthma (y)	15 (6-25)	22 (9-29)	<.001
Family asthma (%)	26	26	.92
Follow-up covariates			
Weight gain (%)	80	73	.12
BMI gain (kg/m²·y)	0.18 (0.04-0.35)	0.15 (0-0.24)	.01
Pack-years between surveys	0 (0-2)	0 (0-4)	.24
Change in ETS (%)			
Unchanged	69	70	.74
Worsened	6	7	
Improved	25	23	

Data are provided as percentages or medians (Q₁-Q₃). Statistically significant results ($P < .05$) are in *boldface*.

(median [Q₁-Q₃], 3.4 [2.9, 4.0] L vs 3.3 [2.8, 4.1] L; $P = .15$), as well as for FEV₁ decline during the follow-up (median [Q₁-Q₃], 29 [7, 50] mL/y vs 29 [10, 52] mL/y; $P = .75$). As shown in [Table I](#), subjects with airflow obstruction at baseline ($n = 94$; 15%) were more likely to be men, to be older, and to have had asthma for a longer time than subjects without airflow obstruction ($n = 544$; 85%). Moreover, they had a lower BMI gain during the follow-up. In subjects without baseline airflow obstruction, a high baseline BMI was associated with a lower baseline FEV₁, both in men and in women ([Fig 1](#)). Obese subjects (BMI range, 30-47 kg/m²) had a lower median FEV₁ than nonobese subjects (3.0 vs 3.5 L; $P < .001$), a lower median FVC (3.8 vs 4.2; $P < .001$) and a lower FEV₁/FVC (0.80 vs 0.82; $P = .10$).

Determinants of lung function decline

FEV₁ decline and %FEV₁/FVC decline were greater for subjects without airflow obstruction than for subjects with airflow obstruction ([Table II](#)).

In subjects with asthma without airflow obstruction at baseline (also see univariate analyses in this article's [Table E1](#) of the Online Repository at www.jacionline.org), FEV₁ decline was associated with baseline BMI in a quadratic way ([Table III, column 1](#)). In other words, men and women with an intermediate BMI had the greatest FEV₁ decline ([Fig 2](#)). Subjects with a high educational level had a faster FEV₁ decline than subjects with a low educational level ($P = .003$; [Table III, column 1](#)). Independently of baseline BMI, FEV₁ decline was 28 mL/y greater for every BMI unit (1 kg/m²) gained during 1 year of follow-up ($P < .001$). Moreover, there was an interaction between sex and BMI

gain ($P = .003$): FEV₁ decline was 61.8 (95% CI, 32.0-91.7; $P < .001$) mL/y greater per BMI unit gained during 1 year of follow-up in men, and 20.2 (95% CI, 7.9-32.6; $P = .001$) mL/y greater per BMI unit gained in women ([Fig 3](#)). This corresponds to a FEV₁ decline of 20.0 (95% CI, 10.4-29.5; $P < .001$) mL/y/kg gained during 1 year of follow-up in men, and to 6.9 (95% CI, 2.5-11.4; $P = .002$) mL/y/kg gained in women.

In subjects with asthma with airflow obstruction at baseline (see this article's [Table E2](#) of the Online Repository at www.jacionline.org), the absence of allergen sensitization ($P = .035$) and a lower BMI ($P = .008$) at baseline were both associated with a faster FEV₁ decline ([Table III, column 2](#)).

No significant association was found between exposure to active or passive smoking and FEV₁ decline, either in subjects with or in subjects without airflow obstruction.

DISCUSSION

A large community-based sample of subjects with asthma was surveyed from 1991 to 93 and again from 1999 to 2002. In the group of individuals without airflow obstruction at baseline, a faster FEV₁ decline was observed in subjects whose BMI was intermediate than for lean and obese subjects. FEV₁ decline was associated with BMI gain independently of baseline BMI, and this association was stronger in men than in women. In the group of individuals with airflow obstruction at baseline, weight gain was not associated with decline.

The analyses were stratified by the presence of airflow obstruction at baseline to account for the heterogeneity of asthma phenotypes.⁴ Because a bronchodilator challenge test was not part of the ECRHS core protocol, we used the follow-up spirometry to confirm baseline airflow obstruction.

The stratification by airflow obstruction at baseline seems to be supported *a posteriori* by our findings, because the role played by BMI and weight gain in FEV₁ decline was different in the 2 groups. Furthermore, a joint *post hoc* analysis (data not reported) showed a significant interaction between BMI gain and the presence of airflow obstruction ($P = .001$).

Compared with subjects with airflow obstruction, subjects without airflow obstruction had a faster FEV₁ decline and %FEV₁/FVC decline during the follow-up. This may be because a steep decline had already occurred before the first visit in subjects with airflow obstruction, as suggested by their lower baseline FEV₁.

Baseline BMI and FEV₁ decline in subjects with asthma without airflow obstruction at baseline

A high baseline BMI was associated with a lower baseline FEV₁, but not with a faster FEV₁ decline during the follow-up. Several studies have reported that obesity decreases lung volumes. In fact, the adipose tissue increases chest wall loading.¹⁷⁻¹⁹ This would also explain the concomitant FVC decline observed in the obese (BMI > 30 kg/m²). However, no evident restrictive pattern (defined by BMI ≥ 30 kg/m² and FEV₁/FVC > 0.70 and FVC < 80% predicted)²⁰ was found at baseline in any of the subjects.

In the absence of a weight reduction, there is no evident reason why the lung function decline in obese subjects should be blunted with respect to nonobese subjects. However, asthma in the obese may be different from asthma in normal-weight subjects. Obesity causes lower than normal functional residual capacity, with the

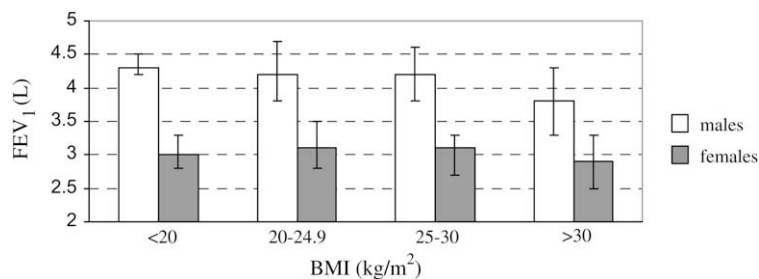


FIG 1. Baseline FEV₁ by categories of baseline BMI for men and women without airflow obstruction at baseline. Medians with Q₁-Q₃ are reported. The number of subjects in the BMI categories <20, 20-24.9, 25-30, and >30 kg/m² are 12, 134, 71, and 7 (men) and 51, 182, 52, and 35 (women), respectively.

TABLE II. Baseline lung function and lung function decline of the subjects with asthma, stratified by the presence of airflow obstruction at baseline

	Airflow obstruction at baseline		P value
	No	Yes	
FEV₁ % predicted (%)	102 (101-103)	78 (75-82)	<.001
FVC % predicted (%)	107 (106-108)	106 (102-110)	.97
FEV₁ (L)*	3.6 (3.5-3.6)	2.7 (2.6-2.8)	<.001
FVC (L)*	4.4 (4.4-4.5)	4.4 (4.3-4.5)	.65
FEV ₁ /FVC†	0.82	0.63	—
FEV₁ decline (mL/y)*	33 (28-37)	23 (14-32)	.04
FVC decline (mL/y)*	22 (15-29)	26 (15-38)	.43
%FEV₁/FVC decline (%/y)†	0.35 (0.29-0.41)	0.16 (0.03-0.29)	.008

Data are provided as means (with 95% CIs). Statistically significant results ($P < .05$) are in **boldface**.

*Adjusted for sex, age, and height.

†Adjusted for sex and age.

consequence of unloading the airway smooth muscle and allowing it to shorten excessively when activated,^{19,21} and a decrease in operational lung volume.²² Moreover, breathing at lower tidal volumes inhibits the bronchodilating effect of tidal strain on the airway smooth muscle.^{19,23} These mechanical and functional changes within the respiratory system may explain the observed link between obesity and bronchial asthma.²⁴ Our data support the hypothesis that asthma in the obese is less determined by inflammation than in the nonobese, in agreement with the reversible nature of lung function decline observed with weight loss.²⁵ This hypothesis, if true, could lead to the implication that, in obese subjects with uncontrolled asthma, weight loss should be primarily targeted, and that it may be worth assessing the level of bronchial inflammation before increasing inhaled steroid doses. However, the faster FEV₁ decline seen in the nonobese compared with the obese could be a result of the fact that obese subjects had a lower baseline FEV₁, and that the process of decline may no longer be progressive after the FEV₁ had previously dropped to a considerable extent.

Obese subjects tend to report doctor-diagnosed asthma, as well as asthmalike symptoms and use of bronchodilators, more frequently than nonobese subjects, even if they do not have an objective impairment of lung function.²⁶ In view of our epidemiologic definition of asthma, one could hypothesize that asthma has been overdiagnosed in the obese subgroup. However, for subjects with BMI <20, BMI 20 to 24.9, BMI 25 to 30, and BMI >30 kg/m², the prevalences of family asthma were 15%, 26%, 29%,

TABLE III. Multiple regression coefficients* with 95% CIs for the association between FEV₁ decline and the covariates indicated in subjects with asthma stratified by the presence of airflow obstruction at baseline

	Airflow obstruction at baseline	
	No (n = 371)†	Yes (n = 76)†
	Estimate (95% CI) (mL/y)	Estimate (95% CI) (mL/y)
Baseline covariates		
BMI (kg/m ²)	11.8 (5.4, 18.2)‡	-4.6 (-8.1, -1.2) ‡
BMI ² [(kg/m ²) ²]	-0.2 (-0.3, -0.09) ‡	—
Low educational level	-18.7 (-30.8, -6.5) ‡	20.2 (-15.2, 55.6)
Pack-years (1-U increase)	-0.2 (-0.6, 0.3)	-0.7 (-2.2, 0.8)
Exposure to ETS	5.9 (-4.4, 16.2)	-29.3 (-62.2, 3.6)
Sensitization to any allergen	-4.0 (-13.1, 5.0)	-29.2 (-56.3, -2.1)
Duration of asthma (y)	-0.3 (-0.7, 0.01)	-0.4 (-1.5, 0.7)
Family asthma	-0.8 (-9.1, 7.6)	-21.4 (-47.8, 5.0)
Follow-up covariates		
BMI gain(kg/[m ² ·y])	28.1 (15.1, 41.1)‡	-7.4 (-51.4, 36.6)
Pack-years between surveys (1-U increase)	-0.2 (-1.3, 1.0)	3.7 (-0.6, 8.0)
Change in ETS		
Worsened vs unchanged	-3.9 (-20.4, 12.6)	26.2 (-23.5, 75.8)
Improved vs unchanged	-6.8 (-17.9, 4.2)	13.7 (-22.6, 50.0)
Intercept§	38.9 (27.2, 50.6)‡	77.1 (44.9, 109.3)‡

Statistically significant results ($P < .05$) are in **boldface**.

*Adjusted also for sex, age, height, and the interaction between total IgE and inhaled steroid use.

†Number of subjects with complete information.

‡ $P < .01$.

§Quantitative variables were centered around their mean to calculate the intercepts; the intercept represents the value of FEV₁ decline when all categorical variables are set to the reference category (eg, sex = male) and all the quantitative variables are set to their mean.

||The estimate for different variables represents the difference in the annual decline in FEV₁ between those with and those without these characteristics (eg, subjects without airflow obstruction at baseline who gained 1 BMI unit per year of follow-up had an additional decline in FEV₁ of 28.1 mL/y compared with those who did not gain weight).

and 35% ($P = .11$), respectively. Thus, this explanation seems unconvincing.

BMI gain and FEV₁ decline in subjects with asthma without airflow obstruction at baseline

In subjects without airflow obstruction, we found that BMI gain during the follow-up was associated with FEV₁ decline, and this

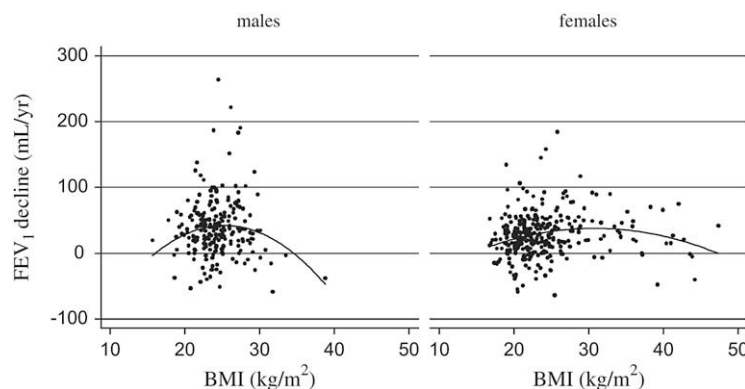


FIG 2. Plot of FEV₁ decline vs baseline BMI, and of the curve representing the FEV₁ decline predicted on the basis of a linear regression on BMI and BMI squared, in men and women without airflow obstruction at baseline.

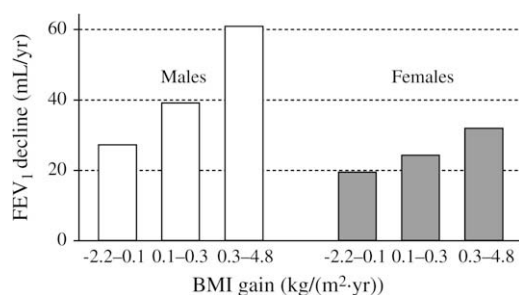


FIG 3. Mean FEV₁ decline (adjusted for all the covariates considered in the multivariate analysis) by categories of BMI gain (according to tertiles) for men and women without airflow obstruction at baseline. *P* value for trend: *P* < .001 (men) and *P* = .001 (women).

association was stronger in men than in women. In men, FEV₁ dropped by 20 (95% CI, 10–30) mL/y for every kilogram gained during the follow-up, whereas in women, FEV₁ decreased by 7 (95% CI, 2–11) mL/y for every kilogram gained. This might be explained by the fact that men who gain weight tend to accumulate abdominal and visceral fat, whereas women who gain weight tend to accumulate peripheral fat.²⁷ Chinn et al¹⁴ found that the FEV₁ decline in the general population of the ECRHS was about 40% lower than the decline we found in the subjects with asthma. Therefore, one could speculate that the negative effect of weight gain on lung function is greater in subjects with asthma than in people from the general population.

The observed association between BMI gain and FEV₁ decline was independent of baseline BMI. This is also confirmed when we consider the group of subjects who were obese at baseline (*n* = 42). Among them, 31 individuals gained weight during the follow-up (median BMI gain [range], 0.5 [0.04, 3.0] kg/m²), and 11 individuals decreased their weight (median BMI gain [range], –0.2 [–2.2, –0.05] kg/m²). FEV₁ decline was faster in the obese subjects who gained weight (median [Q₁–Q₃], 26 [–1, 47] mL/y) than in the obese subjects who decreased their weight (median [Q₁–Q₃], 5 [–38, 34] mL/y; *P* = .13).

Educational level and FEV₁ decline in subjects with asthma without airflow obstruction at baseline

In the population without asthma, a low socioeconomic level is almost universally associated with worse health outcomes,

including lung function.²⁸ In our data, subjects with asthma without airflow obstruction who had a high educational level had a faster FEV₁ decline than those with a lower educational level. However, the latter had a low FEV₁ already at baseline (Table E1). It is possible that a low educational level was associated with an early drop of FEV₁ and that, subsequently, the process of FEV₁ decline was no longer progressive.

Active smoking, passive smoking, and FEV₁ decline in subjects with or without airflow obstruction at baseline

Many^{29–31} but not all³² studies have found that smokers with asthma have a steeper decline in lung function than nonsmokers with asthma. Several factors could explain the lack of an association that was observed in our study. First, our subjects were relatively young, and the detrimental effect of smoking could be greater at older ages.³⁰ Second, the exposure to active smoking of our cohort was relatively low. In the Copenhagen City Heart Study, about 70% of the subjects with asthma were smokers,²⁹ and they had been exposed to smoking for more than 30 years on average.³³ In our study, only 30% were current smokers, and the exposure to active smoking tended to diminish significantly during the follow-up.³⁴ Finally, our finding could reflect the healthy smoker effect.

Determinants of FEV₁ decline in subjects with asthma with airflow obstruction at baseline

Among subjects with airflow obstruction at baseline, those who were not sensitized to allergens had on average 29 mL/y more decline than those who were sensitized to allergens. This is in line with the finding that the rate of lung function decline is greater in subjects with intrinsic asthma than in those with extrinsic asthma,³² and with previous observations.⁷

A 1 kg/m² decrease in baseline BMI was associated with a 5 mL/y decrease in FEV₁ during the follow-up. In this group of subjects with airflow obstruction at baseline, leanness itself may be a marker of an early form of chronic obstructive pulmonary disease.³⁵ No association was found between FEV₁ decline and BMI gain, probably because mechanisms that are typical of milder asthma (including the effect of weight gain) could be less important in severe asthma, whereas a serious long-lasting inflammation

may play a crucial role. Moreover, subjects with airflow obstruction gained on average less weight than those without.

Conclusion

In European subjects with asthma without airflow obstruction at baseline, individuals with a high BMI had the lowest FEV₁ at baseline. Weight gain was positively associated with FEV₁ decline, independently of baseline BMI, and this association was stronger in men than in women. The detrimental effect of BMI gain on lung function might be greater for subjects with asthma than for subjects without asthma, but studies are needed to clarify this. Among subjects with asthma with airflow obstruction at baseline, lean subjects without sensitization to allergens had the greatest FEV₁ decline, whereas weight gain was not associated with FEV₁ decline.

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Clinical implications: Weight management or weight loss should be encouraged in patients with asthma. Asthma in the obese may be different from asthma in the nonobese, possibly because respiratory mechanical factors have a crucial role in the obese.

REFERENCES

- Schünemann HJ, Dorn J, Grant BJ, Winkelstein W Jr, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest* 2000;118:656-64.
- Panizza JA, James AL, Ryan G, de Klerk N, Finucane KE. Mortality and airflow obstruction in asthma: a 17-year follow-up study. *Intern Med J* 2006;36:773-80.
- Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis* 1987;70:171-9.
- James AL, Wenzel S. Clinical relevance of airway remodelling in airway diseases. *Eur Respir J* 2007;30:134-55.
- Dijkstra A, Vonk JM, Jongepier H, Koppelman GH, Schouten JP, ten Hacken NH, et al. Lung function decline in asthma: association with inhaled corticosteroids, smoking and sex. *Thorax* 2006;61:105-10.
- Lange P, Scharling H, Ulrik CS, Vestbo J. Inhaled corticosteroids and decline of lung function in community residents with asthma. *Thorax* 2006;61:100-4.
- de Marco R, Marcon A, Jarvis D, Accordini S, Bugiani M, Cazzoletti L, et al. Inhaled steroids are associated with reduced lung function decline in subjects with asthma with elevated total IgE. *J Allergy Clin Immunol* 2007;119:611-7.
- Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954-60.
- European Community Respiratory Health Survey II Steering Committee. The European Community Respiratory Health Survey II. *Eur Respir J* 2002;20:1071-9.
- American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152:1107-36.
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5-40.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD. 2006. Available at: <http://www.goldcopd.com>. Accessed November 12, 2008.
- Johannessen A, Omenaas ER, Bakke PS, Gulsvik A. Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study. *Thorax* 2005;60:842-7.
- Chinn S, Jarvis D, Melotti R, Luczynska C, Ackermann-Liebrich U, Anto JM, et al. Smoking cessation, lung function, and weight gain: a follow-up study. *Lancet* 2005;365:1629-35.
- Chinn S, Jarvis D, Luczynska CM, Ackermann-Liebrich U, Anto JM, Cerveri I, et al. An increase in bronchial responsiveness is associated with continuing or re-starting smoking. *Am J Respir Crit Care Med* 2005;172:956-61.
- Goldstein H. Multilevel statistical models. 3rd ed. London: Edward Arnold; 2003.
- Zerah F, Harf A, Perlemuter L, Lorino H, Lorino AM, Atlan G. Effects of obesity on respiratory resistance. *Chest* 1993;103:1470-6.
- Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest* 2006;130:827-33.
- Shore SA. Obesity and asthma: possible mechanisms. *J Allergy Clin Immunol* 2008;121:1087-93.
- Lee JH, Haselkorn T, Borish L, Rasouliyan L, Chipps BE, Wenzel SE. Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma: insights from the TENOR study. *Chest* 2007;132:1882-9.
- Ding DJ, Martin JG, Macklem PT. Effects of lung volume on maximal methacholine-induced bronchoconstriction in normal humans. *J Appl Physiol* 1987;62:1324-30.
- Ferretti A, Giampiccolo P, Cavalli A, Milic-Emili J, Tantucci C. Expiratory flow limitation and orthopnea in massively obese subjects. *Chest* 2001;119:1401-8.
- Gump A, Haughey L, Fredberg J. Relaxation of activated airway smooth muscle: relative potency of isoproterenol vs. tidal stretch. *J Appl Physiol* 2001;90:2306-10.
- Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med* 2006;174:112-9.
- Stenius-Aarniala B, Poussa T, Kvarnström J, Grönlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000;320:827-32.
- Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. *Arch Intern Med* 2002;162:1477-81.
- Wise RA, Enright PL, Connett JE, Anthonisen NR, Kanner RE, Lindgren P, et al. Effect of weight gain on pulmonary function after smoking cessation in the Lung Health Study. *Am J Respir Crit Care Med* 1998;157:866-72.
- Hegewald MJ, Crapo RO. Socioeconomic status and lung function. *Chest* 2007;132:1608-14.
- Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194-200.
- Camilli AE, Burrows B, Knudson RJ, Lyle SK, Lebowitz MD. Longitudinal changes in forced expiratory volume in one second in adults: effects of smoking and smoking cessation. *Am Rev Respir Dis* 1987;135:794-9.
- James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, et al. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med* 2005;171:109-14.
- Ulrik CS, Backer V, Dirksen A. A 10 year follow up of 180 adults with bronchial asthma: factors important for the decline in lung function. *Thorax* 1992;47:14-8.
- Lange P, Groth S, Nyboe GJ, Mortensen J, Appleyard M, Jensen G, et al. Effects of smoking and changes in smoking habits on the decline of FEV₁. *Eur Respir J* 1989;2:811-6.
- Janson C, Künzli N, de Marco R, Chinn S, Jarvis D, Svanes C, et al. Changes in active and passive smoking in the European Community Respiratory Health Survey. *Eur Respir J* 2006;27:517-24.
- Agustí AG, Noguera A, Saulea J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J* 2003;21:347-60.

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Project Leader: P. Burney; Statistician: S. Chinn; Principal Investigator: D. Jarvis; Assistant Statistician: J. Potts; Data Manager: S. Arinze.

Steering Committee for ECRHS II

Professor Josep M. Antó, Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra; Professor Peter Burney, Imperial College (Project Leader); Dr Isa Cerveri, University of Pavia; Professor Susan Chinn, King's College London; Professor Roberto de Marco, University of Verona; Professor Thorarinn Gislason, Landspítali University Hospital; Dr Joachim Heinrich, GSF—Institute of Epidemiology; Associate Professor Christer Janson, Uppsala University; Dr Deborah Jarvis, Imperial College; Dr Nino Künzli, Institut Catalana de Recerca i Estudis Avançats and Institut Municipal de Investigació Mèdica, Barcelona; Dr Bénédicte Leynaert, Institut National de la Santé et de la Recherche Médicale; Dr Françoise Neukirch, Institut National de la Santé et de la Recherche Médicale; Dr J. Schouten, University of Groningen; Dr Jordi Sunyer, Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra; Dr Cecilie Svanes, University of Bergen; Dr Matthias Wjst, GSF—Institute of Epidemiology.

List of Principal Investigators and Senior Scientific Team

Belgium: South Antwerp and Antwerp City (J. Weyler, M. Van Sprundel, V. Nelen). Estonia: Tartu (R. Jogi, A. Soon). France: Paris (F. Neukirch, B. Leynaert, R. Liard, M. Zureik), Grenoble (I. Pin, J. Ferran-Quentin). Germany: Erfurt (J. Heinrich, M. Wjst, C. Frye, I. Meyer). Iceland: Reykjavik (T. Gislason, E. Bjornsson, D. Gislason, T. Blondal, K. B. Jorundsdottir). Italy: Turin (M. Bugiani, P. Piccioni, E. Caria, A. Carosso, E. Migliore, G. Castiglioni), Verona (R. de Marco, G. Verlato, E. Zanolin, S. Accordini, A. Poli, V. Lo Cascio, M. Ferrari), Pavia (A. Marinoni, S. Villani, M. Ponzio, M. Comelli, M. Grassi, I. Cerveri, A. Corsico). Norway: Bergen (A. Gulsvik, E. Omenaas, C. Svanes, B. Laerum). Spain: Barcelona (J. M. Antó, J. Sunyer, M. Kogevinas, J. P. Zock, X. Basagana, A. Jaen, F. Burgos), Huelva (J. Maldonado, A. Pereira, J. L. Sanchez), Albacete (J. Martinez-Moratalla Rovira, E. Almar), Galdakao (N. Muniozguren, I. Urritia), Oviedo (F. Payo). Sweden: Uppsala (C. Janson, G. Boman, D. Norback, M. Gunnbjornsdottir), Goteborg (K. Toren, L. Lillienberg, A. C. Olin, B. Balder, A. Pfeifer-Nilsson, R. Sundberg), Umea (E. Norrman, M. Soderberg, K. Franklin, B. Lundback, B. Forsberg, L. Nystrom). Switzerland: Basel (N. Künzli, B. Dibbert, M. Hazenkamp, M. Brutsche, U. Ackermann-Liebrich). United Kingdom: Norwich (D. Jarvis, B. Harrison), Ipswich (D. Jarvis, R. Hall, D. Seaton).

Centers taking part at their own expense

France: Bordeaux (A. Taytard, C. Raherison), Montpellier (J. Bousquet, P. Demoly). Germany: Hamburg (K. Richter). United States: Portland (M. Osborne, S. Buist, W. Vollmer, L. Johnson).

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TABLE E1. Median FEV₁ at baseline, median FEV₁ decline during the follow-up for subjects with asthma without airflow obstruction, according to different characteristics (quantitative variables have been categorized*), and *P* value for the association between the characteristics and FEV₁ decline

	Median FEV ₁ (L)	Median FEV ₁ decline (mL/y)	<i>P</i> value
Baseline covariates			
BMI (kg/m²)			<.001
<20	3.1	20	
20-24.9	3.5	28	
25-29.9	3.6	37	
≥30	3.0	23	
Educational level			.09
High	3.5	30	
Low	3.1	23	
Pack-years			.006
0	3.4	28	
0.1-8.9	3.5	22	
≥9	3.4	35	
Exposure to ETS			.32
Present	3.4	28	
Absent	3.4	31	
Sensitization to any allergen			.05
Present	3.4	35	
Absent	3.4	26	
Duration of asthma (y)			.88
<15.7	3.3	29	
≥15.7	3.6	30	
Family asthma			.12
Present	3.5	29	
Absent	3.3	33	
Follow-up covariates			
BMI gain (kg/[m²·y])			.001
−2.2 to 0.1	3.4	21	
0.2 to 0.3	3.5	32	
0.4 to 4.8	3.3	32	
Pack-years between surveys			.74
0	3.4	28	
<5.5	3.6	30	
≥5.5	3.5	32	
Change in ETS			.57
Unchanged	3.4	30	
Worsened	3.4	28	
Improved	3.5	29	

Variables whose association was statistically significant (*P* < .05) are in *boldface*.

*Values used for the categorization: pack-years at baseline/during the follow-up (0 and the median for subjects who smoked in the period considered), duration of asthma (median), and BMI gain (tertiles). The quantiles were calculated on the whole sample (subjects with + without airflow obstruction).

TABLE E2. Median FEV₁ at baseline, median FEV₁ decline during the follow-up for subjects with asthma with airflow obstruction, according to different characteristics (quantitative variables have been categorized*), and *P* value for the association between the characteristics and FEV₁ decline

	Median FEV ₁ (L)	median FEV ₁ decline (mL/year)	<i>P</i> value
Baseline covariates			
BMI (kg/m ²)			.35
<20	3.0	35	
20-24.9	3.0	30	
25-29.9	3.0	24	
≥30	2.1	8	
Educational level			.58
High	3.1	23	
Low	2.0	38	
Pack-years			.39
0	2.7	28	
0.1-8.9	2.7	27	
≥9	3.1	37	
Exposure to ETS			.93
Present	2.9	32	
Absent	2.9	26	
Sensitization to any allergen			.16
Present	3.0	39	
Absent	2.9	30	
Duration of asthma (y)			
<15.7	3.0	23	
≥15.7	2.9	33	.56
Family asthma			.21
Present	3.0	39	
Absent	2.7	19	
Follow-up covariates			
BMI gain (kg/[m ² ·y])			.82
−2.2 to 0.1	2.7	32	
0.2 to 0.3	3.0	31	
0.4 to 4.8	2.8	23	
Pack-years between surveys			
0	2.7	16	
<5.5	3.1	23	.03
≥5.5	3.1	56	
Change in ETS			.65
Unchanged	2.9	30	
Worsened	3.0	33	
Improved	2.7	26	

Variables whose association was statistically significant (*P* < .05) are in *boldface*.

*Values used for the categorization: pack-years at baseline/during the follow-up (0 and the median for subjects who smoked in the period considered), duration of asthma (median), and BMI gain (tertiles). The quantiles were calculated on the whole sample (subjects with + without airflow obstruction).