

Original article

The socio-economic burden of asthma is substantial in Europe

Background: Few data are available on the asthma burden in the general population. We evaluated the level and the factors associated with the asthma burden in Europe.

Methods: In 1999–2002, 1152 adult asthmatics were identified in the European Community Respiratory Health Survey (ECRHS)-II and the socio-economic burden (reduced activity days and hospital services utilization in the past 12 months) was assessed.

Results: The asthmatics with a light burden (only a few reduced activity days) were 13.2% (95% CI: 11.4–15.3%), whereas those with a heavy burden (many reduced activity days and/or hospital services utilization) were 14.0% (95% CI: 12.1–16.1%). The burden was strongly associated with disease severity and a lower quality of life. Obese asthmatics had a significantly increased risk of a light [relative risk ratio (RRR) = 2.17; 95% CI: 1.18–4.00] or a heavy burden (RRR = 2.77; 95% CI: 1.52–5.05) compared with normal/underweight subjects. The asthmatics with frequent respiratory symptoms showed a threefold (RRR = 2.74; 95% CI: 1.63–4.61) and sixfold (RRR = 5.76; 95% CI: 3.25–10.20) increased risk of a light or a heavy burden compared with asymptomatic asthmatics, respectively. Moreover, the lower the forced expiratory volume in 1 s (% predicted), the higher the risk of a heavy burden. The coexistence with chronic cough/phlegm only increased the risk of a heavy burden (RRR = 1.88; 95% CI: 1.16–3.06). An interaction was found between gender and IgE sensitization, with nonatopic asthmatic females showing the highest risk of a heavy burden (21.6%; 95% CI: 16.9–27.1%).

Conclusions: The asthma burden is substantial in Europe. A heavy burden is more common in asthmatics with obesity, frequent respiratory symptoms, low lung function, chronic cough/phlegm and in nonatopic females.

S. Accordini¹, A. Corsico², I. Cerveri², D. Gislason³, A. Gulsvik⁴, C. Janson⁵, D. Jarvis⁶, A. Marcon¹, I. Pin⁷, P. Vermeire⁸, E. Almar⁹, M. Bugiani¹⁰, L. Cazzoletti¹, E. Duran-Tauleria¹¹, R. Jögi¹², A. Marinoni¹³, J. Martínez-Moratalla¹⁴, B. Leynaert¹⁵, R. de Marco¹; Therapy and Health Economics Working Group of the European Community Respiratory Health Survey II

¹Unit of Epidemiology and Medical Statistics, Department of Medicine and Public Health, University of Verona, Verona, Italy; ²Division of Respiratory Diseases, Istituto di Ricovero e Cura a Carattere Scientifico "San Matteo" Hospital, University of Pavia, Pavia, Italy; ³Department of Allergy, Respiratory Medicine and Sleep, Landspítali University Hospital, Reykjavik, Iceland; ⁴Department of Thoracic Medicine, Haukeland University Hospital, University of Bergen, Bergen, Norway; ⁵Department of Medical Sciences, Respiratory Medicine and Allergology, Uppsala University, Uppsala, Sweden; ⁶Respiratory Epidemiology and Public Health Group, National Heart and Lung Institute, Imperial College, London, UK; ⁷Department of Pediatrics, Centre Hospitalier Universitaire and INSERM U578 U823, Institut Albert Bonniot, Centre Hospitalier Universitaire de Grenoble, Grenoble, France; ⁸Campus Drie Eiken, University of Antwerp, Antwerp, Belgium; ⁹Unit of Epidemiology, Public Health Department of Castilla La Mancha, Albacete, Spain; ¹⁰Unit of Pneumology, Consorzio Provinciale Antitubercolare, Azienda Sanitaria Locale 4 Piemonte, Turin, Italy; ¹¹Institut Municipal d'Investigació Mèdica (IMIM), Universitat Pompeu Fabra (UPF), Barcelona, Spain; ¹²Foundation Tartu University Clinics, Lung Clinic, Tartu, Estonia; ¹³Department of Applied Health Sciences, Faculty of Medicine, University of Pavia, Pavia, Italy; ¹⁴Servicio de Neumología, Complejo Hospitalario Universitario de Albacete, Servicio de Salud de Castilla-La Mancha, Albacete, Spain; ¹⁵Epidémiologie des Maladies Respiratoires, INSERM U700, Faculté de Médecine Xavier Bichat, Paris, France

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Dott. Simone Accordini
Sezione di Epidemiologia & Statistica Medica
Dipartimento di Medicina e Sanità Pubblica
Università degli Studi di Verona
c/o Istituti Biologici II
Strada Le Grazie 8
37134 – Verona, Italy

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Abbreviations: 95%CI, 95% confidence interval; BMI, body mass index; ECRHS, European Community Respiratory Health Survey; ED, emergency department; FEV₁, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; HRQL, health-related quality of life; IgE, immunoglobulin E; IQR, interquartile range; kU/l, kilo units/liter; MCS, mental component summary; PCS, physical component summary; RRR, relative risk ratio.

Bronchial asthma is a common chronic disease (1) that remains poorly controlled for many patients, generating a high socio-economic burden in industrialized countries (2). While the major outcome measures of disease control in asthma must be clinical endpoints, the burden of the disease may be defined in terms of costs to the patient and society (3).

According to the Global Initiative for Asthma (GINA) guidelines on asthma management and prevention (4), well-treated patients are expected to have not only minimal chronic symptoms and exacerbations, but also no emergency visits and no limitation of their daily activities. Recently, the Gaining Optimal Asthma control (GOAL) study has shown that a guideline-defined control of asthma can be achieved with appropriate treatment in the majority of patients, regardless of the severity of their disease (5). However, few data are available on the management of asthma in the general population (6–9), and even fewer data are available on the factors that can be related to the burden of asthma and to the most impairing forms of the disease.

The aim of this study was: (i) to evaluate the socio-economic burden of asthma, in terms of reduced activity days and acute disease-related healthcare resource utilization, in adult asthmatic subjects from the general population in Europe; (ii) to evaluate the factors related to the most impairing forms of the disease. To reach these goals, the data from the repeat of the European Community Respiratory Health Survey (ECRHS II) (10) were used.

Methods

Study design

The present analysis is a cross-sectional evaluation of the socio-economic burden of the disease in the asthmatic subjects identified in the ECRHS II in Europe. The ECRHS II is a follow-up study of the subjects who were previously investigated in the second stage of the ECRHS I (11). The ECRHS I was a multi-centre cross-sectional survey on respiratory health carried out between 1991 and 1993 on random samples of adults aged 20–44 from the general population. Each participant was sent a brief questionnaire (stage 1); a 20% random sample of the responders and a 'symptomatic sample', consisting of those who had reported nocturnal shortness of breath or asthma attacks in the past 12 months or who had reported taking asthma medication, was invited to undergo a more detailed clinical examination (stage 2).

The follow-up of the participants in the second stage of the ECRHS I was carried out between 1999 and 2002 (the full protocol is available at the ECRHS web site: <http://www.ecrhs.org>; accessed 22 August 2007) (10). The subjects involved in the ECRHS II underwent an extended clinical interview, spirometry according to the American Thoracic Society guidelines (12), and the measurement of serum total and specific IgE to *Dermatophagoides pteronyssinus*, cat, timothy grass and *Cladosporium herbarum*. Ethical approval was obtained for each centre from the appropriate ethics committee and written consent was obtained from each participant.

Subjects and definitions

The subjects considered in the analysis were the 1152 individuals with complete information on the burden of the disease (reduced activity days and use of hospital services) in the ECRHS II, who had reported asthma confirmed by a doctor and at least one respiratory symptom (wheezing, nocturnal tightness in the chest, attacks of shortness of breath following strenuous activity, at rest or at night time) or at least one attack of asthma or use of medicines because of breathing problems in the past 12 months at the clinical interview (Table 1). These subjects were single out among the 9580 participants in the ECRHS II in 11 European countries (61.0% of the subjects involved in the ECRHS I and eligible for the ECRHS II in the 11 countries), from both the random and symptomatic samples.

The burden of asthma was classified as a three-level variable according to the answers to a set of questions on leisure time forgone (number of days with limited, not work related activities, such as looking after children, the house, studying), productivity losses (number of lost working days) and use of hospital services [number of Emergency Department (ED) visits and number of nights spent in hospital] because of breathing problems in the past 12 months at the clinical interview, that is:

- *No burden*: no productivity losses/leisure time forgone and no use of hospital services in the past 12 months;
- *Light burden*: low productivity losses/leisure time forgone (i.e. up to 12 lost working days and/or up to 3 days per month with limited, not work related activities) but no use of hospital services in the past 12 months;

Table 1. Number of asthmatic subjects considered in this analysis by centre and type of sample at the ECRHS I

Country	Centre	No. of asthmatic subjects from the random sample (%)	No. of asthmatic subjects from the symptomatic sample (%)	Total
Iceland	Reykjavik	38 (50.7)	37 (49.3)	75
Norway	Bergen	27 (100.0)	-	27
Sweden	Goteborg	40 (47.1)	45 (52.9)	85
	Umea	43 (35.8)	77 (64.2)	120
	Uppsala	39 (32.0)	83 (68.0)	122
Estonia	Tartu	4 (30.8)	9 (69.2)	13
UK	Ipswich	35 (46.1)	41 (53.9)	76
	Norwich	35 (49.3)	36 (50.7)	71
Germany	Erfurt	23 (100.0)	-	23
	Hamburg	25 (100.0)	-	25
Belgium	Antwerp City	16 (61.5)	10 (38.5)	26
	Antwerp South	10 (50.0)	10 (50.0)	20
Switzerland	Basel	32 (40.5)	47 (59.5)	79
France	Bordeaux	23 (100.0)	-	23
	Grenoble	34 (58.6)	24 (41.4)	58
	Montpellier	21 (100.0)	-	21
	Paris	43 (100.0)	-	43
Spain	Albacete	18 (34.6)	34 (65.4)	52
	Barcelona	14 (31.1)	31 (68.9)	45
	Galdakao	12 (27.3)	32 (72.7)	44
	Huelva	11 (37.9)	18 (62.1)	29
	Oviedo	13 (38.2)	21 (61.8)	34
Italy	Pavia	7 (100.0)	-	7
	Turin	8 (47.1)	9 (52.9)	17
	Verona	13 (76.5)	4 (23.5)	17
Total		584 (50.7)	568 (49.3)	1152

- *Heavy burden*: high productivity losses/leisure time forgone (i.e. more than 12 lost working days and/or more than 3 days per month with limited, not work related activities) and/or use of hospital services (i.e. at least one ED visit and/or at least one night spent in hospital) in the past 12 months.

The days with limited, not work related activities (such as looking after children or the house) reported by full-time house-persons were considered as lost working days.

The subjects considered in the analysis were also classified according to a set of potential predictors of the burden of the disease measured at the ECRHS II. Besides gender and age, the following socio-demographic characteristics and exposures were considered:

- Body Mass Index (BMI) ('normal/underweight', BMI < 25.0 kg/m²; 'overweight', 25.0 ≤ BMI < 30.0 kg/m²; 'obese', BMI ≥ 30.0 kg/m²);
- Low socio-economic class (having completed full-time education before the age of 16);
- Smoking habits ('nonsmoker'; 'past smoker'; 'current smoker'; subjects were considered smokers – current or past – if they reported at least 20 packs of cigarettes or 360 g of tobacco in a lifetime, or at least one cigarette per day or one cigar a week for 1 year);
- A history of occupational exposure to dusts, gases or fumes (13);
- Frequent passage of heavy vehicles – trucks, buses – near home (reported at the clinical interview, as a proxy of a high level of air pollution).

In addition, the following clinical and functional variables were taken into account:

- Age at asthma onset;
- Frequency of nocturnal and diurnal respiratory symptoms (how many times a subject has woken up and has had trouble with breathing because of his/her asthma) in the past 3 months ('absent'; 'occasional', if nocturnal symptoms were reported less than twice a month and/or if diurnal symptoms were reported less than once a week; 'frequent', if nocturnal symptoms were reported at least twice a month and/or if diurnal symptoms were reported at least once a week);
- Lung function [measured by the forced expiratory volume in 1 s (FEV₁) % predicted, considering the maximum FEV₁ from at least two and up to five technically satisfactory manoeuvres; predicted values were from Quanjer (14)];
- IgE sensitization (having at least one specific IgE measurement ≥ 0.35 kU/l among the four environmental allergens – *D. pteronyssinus*, cat, timothy grass and *C. herbarum*);
- Chronic cough or phlegm (having reported cough and/or phlegm from the chest, usually in winter and on most days for as long as 3 months each year);
- Allergic rhinitis (having reported any nasal allergies, including hay fever).

The subjects' health-related quality of life (HRQL) was measured by means of the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores from the SF-36 questionnaire (version 1.3) (15). The PCS and MCS scores were computed as recommended by developers (16, 17). The severity of asthma was defined according to the GINA guidelines (18) as a 4-step scale ('intermittent', 'mild persistent', 'moderate persistent', 'severe persistent'), which was obtained through a combination of the clinical severity (lung function and frequency of nocturnal and diurnal symptoms) and the daily treatment received (type and dosage of drugs, mainly inhaled corticosteroids).

Statistical analysis

Data were reported as percentages with the 95% confidence interval, adjusting for type of sample (random or symptomatic) because of the different criteria of selection through logistic regression models (considering the variable of interest as the dependent variable and type of sample as a covariate).

A two-level multinomial logit model (19) with level 1 units (subjects) nested into level 2 units (ECRHS II centres crossed by type of sample) was used to assess the association between the burden of asthma and the socio-demographic characteristics, exposures, clinical and functional variables considered in the analysis. The model had an indicator of the burden of the disease (0 = no burden, 1 = light burden, 2 = heavy burden) as the dependent variable, different random intercept terms at level 2 and all the predictor variables as fixed effects. The strength of the association between each predictor variable and the burden of the disease was measured through mutually adjusted relative risk ratios (RRRs).

Pearson's chi-squared test, Kruskal–Wallis rank test, score test for trend of odds adjusted for type of sample and likelihood-ratio test after estimation were used when needed.

The statistical analysis was performed using STATA software, release 9.2 (StataCorp, College Station, TX, USA).

Results

In the European countries involved in the ECRHS II, the asthmatic subjects who reported a light burden because of their disease in the past 12 months were 13.2% (95% CI: 11.4–15.3%), whereas those with a heavy burden were 14.0% (95% CI: 12.1–16.1%). The remaining subjects (72.8%) did not report reduced activity days nor acute disease-related healthcare resource utilization in the past 12 months. The percentage of individuals with a light burden was similar in the random and symptomatic samples (12.8% vs 13.6%; $P = 0.720$), whereas the figure for the heavy burden was significantly higher in the latter (11.8% vs 16.5%; $P = 0.021$). Overall, 13.2% of the asthmatic subjects reported at least one day with limited, not work related activities (median = 24 days; interquartile range, IQR: 12–60 days), 16.4% at least one lost working day (median = 7 days; IQR: 3–14 days), 7.1% at least one ED visit (median = 1 visit; IQR: 1–2 visits) and 2.0% at least one night spent in hospital (median = 1.5 nights; IQR: 1–6 nights) because of breathing problems in the past 12 months.

The asthmatic subjects with a heavy burden were characterized by the highest percentage of obese patients (BMI ≥ 30.0 kg/m²) (Table 2). Among the main clinical and functional variables considered in the analysis, respiratory symptoms were significantly associated with the burden of the disease (Table 3); in fact, an increasing trend was observed for the percentage of subjects with a light or a heavy burden according to the frequency of symptoms (Fig. 1). A negative association was found for IgE sensitization

Table 2. Distribution of the main socio-demographic characteristics and exposures measured at the ECRHS II, according to the burden of asthma in the past 12 months

	No burden (n = 837)	Light burden (n = 152)	Heavy burden (n = 163)	Total (n = 1152)	P-value
Females (%)	57.0	56.6	65.0	58.1	0.151
Age (years) (%)					
27.5–37.5	32.3	27.6	35.6	32.1	0.552
37.5–47.5	39.4	39.5	35.6	38.9	
47.5–57.5	28.3	32.9	28.8	29.0	
Body Mass Index (%)					
normal/underweight*	51.3	39.5	43.4	48.6	< 0.001
overweight	35.3	36.6	29.4	34.7	
obese	13.4	23.9	27.2	16.7	
Low socio-economic class (%)	22.0	24.5	30.9	23.6	0.048
Smoking habits (%)					
nonsmokers	48.6	44.7	47.9	48.0	0.559
past smokers	25.8	30.9	23.3	26.1	
current smokers	25.6	24.4	28.8	25.9	
Occupational exposure (%)					
absent	54.8	53.4	52.0	54.3	0.265
low	33.0	33.6	29.1	32.5	
high	12.2	13.0	18.9	13.2	
Heavy traffic near home (%)	27.6	30.3	36.2	29.2	0.083

*Twenty-two subjects (2.2%) were underweight (BMI <18.5 kg/m²).

and lung function (measured by the FEV₁% predicted). The percentage of asthmatic subjects with a heavy burden was particularly high among those with low lung function (Fig. 2), being 20.4% among the patients with a FEV₁ ≤ 80% predicted and 31.1% considering only those with a FEV₁ ≤ 65% predicted. Moreover, a positive association was observed for coexisting chronic cough or phlegm.

The asthmatic subjects with a heavy burden were characterized by the highest percentage of patients with

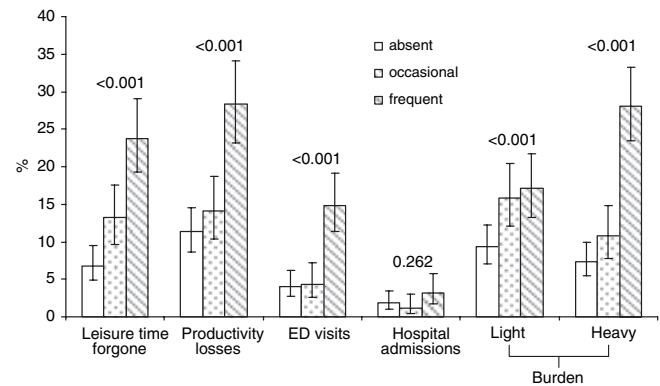


Figure 1. Percentage of asthmatic subjects with a light or a heavy burden in the past 12 months, according to the frequency of respiratory symptoms. All the percentages are adjusted for type of sample (random or symptomatic). P-values for trend of odds adjusted for type of sample are reported.

severe persistent asthma, as defined by the GINA guidelines, and by the highest percentage of patients with a low HRQL for both the PCS and MCS scores (Table 4). These individuals reported a higher use of drugs (mainly inhaled steroids) (93.3%), a higher frequency of doctor visits (86.7%) and a higher frequency of spirometry tests (27.8%) in the past 12 months, than the subjects who had only a few reduced activity days (82.8%, 75.6% and 13.2%, respectively) and those who reported no burden (71.9%, 41.4% and 9.5%, respectively) ($P < 0.001$).

In a multivariate analysis, obese asthmatics showed a significantly increased risk of having productivity losses/leisure time forgone or of using hospital services compared with normal/underweight subjects, with no statistically significant effect modification due to gender (Table 5). The asthmatic individuals with frequent respiratory symptoms had a threefold and sixfold

Table 3. Distribution of the main clinical and functional variables measured at the ECRHS II, according to the burden of asthma in the past 12 months

	No burden (n = 837)	Light burden (n = 152)	Heavy burden (n = 163)	Total (n = 1152)	P-value
Age at onset (years) (%)					
0–10	28.8	24.8	27.1	28.0	0.689
10–20	22.9	27.5	22.0	23.4	
≥20	48.3	47.7	50.9	48.6	
Respiratory symptoms (%)					
absent	52.5	32.4	23.5	45.8	<0.001
occasional	26.8	31.8	21.0	26.6	
frequent	20.7	35.8	55.5	27.6	
Median FEV ₁ % predicted (IQR *)	99.5 (88.7–109.3)	96.0 (86.5–106.0)	96.1 (82.2–106.0)	98.8 (87.4–108.0)	0.008
IgE sensitization (%)	67.0	56.5	52.2	63.4	0.001
Chronic cough or phlegm (%)	22.0	30.0	45.1	26.3	<0.001
Allergic rhinitis (%)	65.4	68.9	69.3	66.4	0.491

*IQR = interquartile range.

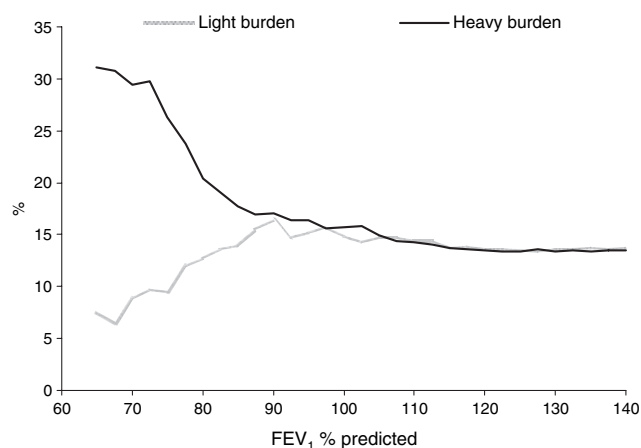


Figure 2. Percentage of asthmatic subjects with a light or a heavy burden in the past 12 months, according to lung function (measured by the FEV₁% predicted). Percentages are computed considering the subjects who had a FEV₁ ≤ X predicted at the ECRHS II, where X ranges from 65% to 140%. Only subjects with valid lung function measurements are considered. All the percentages are adjusted for type of sample (random or symptomatic).

Table 4. Distribution of asthma severity, as defined by the GINA guidelines, and health-related quality of life (HRQL, Physical and Mental Component Summary scores from the SF-36 questionnaire) measured at the ECRHS II, according to the burden of asthma in the past 12 months

	No burden (n = 837)	Light burden (n = 152)	Heavy burden (n = 163)	Total (n = 1152)	P-value
GINA severity (%):					
severe persistent	14.5	25.3	45.9	20.2	<0.001
moderate persistent	16.4	12.7	15.7	15.8	
mild persistent	9.4	14.8	11.0	10.4	
intermittent	59.7	47.2	27.4	53.6	
Low HRQL – Physical Component Summary (%)*	17.5	35.8	55.0	25.0	<0.001
Low HRQL – Mental Component Summary (%)*	21.7	31.3	36.4	25.0	<0.001

*HRQL data available from 973 asthmatic subjects; low HRQL defined as having a PCS score or a MCS score below the first quartile observed in the whole sample.

increased risk of reporting a light or a heavy burden compared with asymptomatic subjects, respectively. Moreover, the lower the FEV₁% predicted, the higher the risk of a heavy burden. The coexistence with chronic cough or phlegm was positively associated with a heavy burden only.

A statistically significant interaction was found between gender and IgE sensitization, with a threefold increased risk of a heavy burden for nonatopic females compared with nonatopic males (Table 5). The effect modification due to gender is described in Fig. 3.

Table 5. Mutually adjusted relative risk ratios (RRRs)[†] for the risk of reporting a light or a heavy burden in the past 12 months

	Light burden RRR (95%CI)	Heavy burden RRR (95%CI)
Body Mass Index		
normal/underweight	1.00	1.00
overweight	1.29 (0.79–2.10)	0.91 (0.54–1.55)
obese	2.17 (1.18–4.00)*	2.77 (1.52–5.05)**
Low socio-economic class	0.81 (0.48–1.36)	1.22 (0.72–2.06)
Smoking habits		
nonsmoker	1.00	1.00
past smoker	1.32 (0.78–2.21)	1.02 (0.59–1.79)
current smoker	1.24 (0.72–2.14)	0.78 (0.44–1.38)
Occupational exposure		
absent	1.00	1.00
low	1.03 (0.64–1.65)	0.91 (0.55–1.51)
high	1.13 (0.57–2.26)	1.83 (0.92–3.63)
Heavy traffic near home	1.12 (0.70–1.78)	1.32 (0.81–2.15)
Respiratory symptoms		
absent	1.00	1.00
occasional	1.43 (0.83–2.45)	2.16 (1.16–4.02)*
frequent	2.74 (1.63–4.61)**	5.76 (3.25–10.20)**
FEV ₁ % predicted (1% change)	1.00 (0.99–1.01)	0.99 (0.97–1.00)*
Chronic cough or phlegm	1.32 (0.81–2.15)	1.88 (1.16–3.06)*
Allergic rhinitis	1.03 (0.65–1.66)	1.19 (0.72–1.95)
Gender × IgE sensitization		
male without IgE sensitization	1.00	1.00
female without IgE sensitization	0.74 (0.35–1.56)	3.16 (1.29–7.77)*
male with IgE sensitization	0.49 (0.24–1.00)*	1.16 (0.48–2.82)
female with IgE sensitization	0.53 (0.25–1.12)	1.08 (0.42–2.75)

* $P < 0.05$; ** $P < 0.001$.

[†]also adjusted for age and age at onset through a two-level multinomial logit model with level 1 units (subjects) nested into level 2 units (ECRHS II centres crossed by type of sample), only taking the 819 asthmatic subjects with complete information on all the covariates into account.

Overall, the percentage of asthmatic individuals with any level of the burden was higher among those without IgE sensitization than among atopic subjects (34.6% vs 23.5%; $P < 0.001$). Among the asthmatic individuals without IgE sensitization, the risk of a heavy burden was higher for females (21.6%; 95% CI: 16.9–27.1%), whereas the risk of a light burden was higher for males (22.3%; 95% CI: 15.0–31.8%). Accordingly, females without IgE sensitization had a lower HRQL (percentage of subjects with a PCS score and a MCS score below the first quartile: 34.1% and 38.6%, respectively) when compared with nonatopic males (26.8%, 15.9%), and with atopic males (18.2%, 17.8%) and females (21.8%, 23.4%) ($P \leq 0.001$). Females without IgE sensitization were characterized by a later onset of their disease (median age: 27.0 years) when compared with nonatopic males (21.5 years), and with atopic males (12.0 years) and females (18.0 years) ($P < 0.001$). Moreover, the frequency of chronic cough or phlegm was significantly higher among those without IgE sensitization than among atopic subjects (36.5% vs 21.4%; $P < 0.001$).

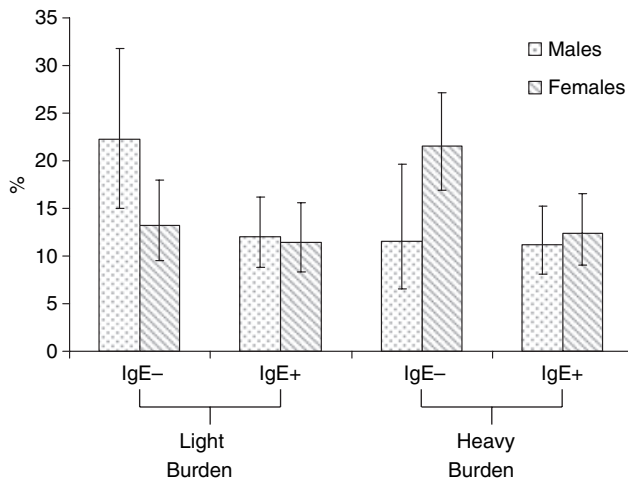


Figure 3. Percentage of asthmatic subjects with a light or a heavy burden in the past 12 months, according to gender and IgE sensitization. All the percentages are adjusted for type of sample (random or symptomatic). IgE-, asthmatic subjects without IgE sensitization; IgE+, asthmatic subjects with IgE sensitization.

Discussion

The results of our analysis point out that among adult asthmatic individuals from the general population in Europe:

- The socio-economic burden of the disease is substantial;
- Obese subjects report high productivity losses/leisure time forgone or hospital services utilization more frequently than nonobese patients;
- Frequent symptoms of asthma, low lung function and coexisting chronic cough or phlegm are significantly associated with an increased risk of a heavy burden;
- Nonatopic females seem to suffer from a more impairing form of the disease than males and atopic females.

In this study, about one of four asthmatic subjects from the general population reported leisure time forgone, productivity losses or use of hospital services because of his/her disease in the past 12 months. Furthermore, the burden of the disease was negatively associated with the subjects' HRQL for both the PCS and MCS scores, as the lower the HRQL, the heavier the burden. This is not surprising as inappropriate treatment, poor treatment adherence and poor control of asthma have been repeatedly reported since the early 1990s (7, 20–24), with negative consequences on patients' quality of life (25) and with a substantial burden on patients and society (26, 27). At variance with this negative picture, a clinical trial (5) showed

that a guideline-defined control of asthma can be achieved in the majority of patients with the appropriate treatment. Moreover, a good control of asthma is also achievable in the daily management of the disease when the use of drugs follows the guideline recommendations (9). The difference between what can be achieved with widespread available anti-asthmatic therapy and the observed level of the asthma burden renews the emphasis upon the need for better management of the disease in real life.

As expected, the burden of the disease was strongly associated with a subjective indicator of poor control, such as self-reported nocturnal and diurnal symptoms of asthma, which reflects the adequacy of current treatment (28), but may be influenced by a patient's perception and recognition of symptoms and of their severity (29). However, also an objective indicator of control, such as FEV₁, was significantly associated with higher limitations to asthmatic patients' daily life. In our opinion, this result is particularly important because it supports the GINA guidelines in recommending the use of spirometry to establish a diagnosis of asthma and to assess the control of the disease (4). Furthermore, the subjects with a heavy burden had a more severe disease, as indicated by the GINA severity classification based on clinical features and daily medication regimen, than the individuals with only a few reduced activity days and those who reported no burden. However, the relationship between the treatment received by the patients and the burden of the disease cannot be clarified due to the cross-sectional nature of our study. In fact, the higher use of drugs (mainly inhaled steroids) in the past 12 months reported by the subjects with a heavy burden could be explained by a 'reverse causation bias', that is, the asthmatic patients with uncontrolled asthma generally receive a higher step of treatment than the subjects with a good control, or could suggest that the treatment was inappropriate in relation to asthma severity or that the achievement of control may be over-ambitious.

In addition, we found a positive association between coexisting chronic cough or phlegm and the risk of a heavy burden. This symptom is often a sign that asthma is not properly controlled (7), with consequent high economic costs (27), and it is a marker of a more severe level of the disease (30). Alternatively, the presence of chronic cough or phlegm, which identifies a subgroup of subjects with a high risk of developing chronic obstructive pulmonary disease (COPD), independently of smoking habits (31), could indicate the most difficult patients to treat, who may have the coexistence of asthma and COPD (32).

Besides the current clinical status and drug-related factors, also intrinsic individual characteristics, such as obesity and IgE sensitization, were associated with the burden of the disease. Obese asthmatics had a twofold increased risk of having low productivity losses/leisure

time forgone only and a threefold increased risk of reporting a heavier burden. This finding is in agreement with a recent study, which indicates that having a higher BMI may complicate asthma control and quality of life, independently of age, gender and asthma severity (33). Obese subjects may have behavioural difficulties regarding the self-management of asthma and diet (33), and may have mechanical limitations due to decreased lung volume and reduced airway calibre (34, 35). Our data show that only being overweight, which has probably no relevant effect on lung function, is not associated with an increased risk of reporting a burden at any level, while obese asthmatic subjects should be regarded as a particular category.

The percentage of atopic subjects significantly decreased according to the level of the burden. This finding is not surprising because the clinical course of nonallergic asthma in adults is often more severe than that of allergic asthma (36). Owing to a statistically significant interaction between gender and IgE sensitization, the threefold increased risk of reporting a heavy burden for nonatopic females compared with nonatopic males, requires further comments. Romanet-Manent et al. found that females had a fivefold increased risk of having nonallergic asthma when compared with allergic asthma (36). We found that nonatopic females had a later onset when compared with males and atopic females, and a higher frequency of chronic cough or phlegm when compared with atopic individuals, factors that are associated with a poor prognosis (30, 37). Nonallergic asthma also includes aspirin-induced asthma, which is more progressive and severe in females than in males (38). Thus, it is possible that females have a more severe form of the disease than males, at least in the case of nonallergic asthmatics (39). Furthermore, the asthmatic subjects with low IgE are less responsive to a prolonged use of inhaled steroids than those with high IgE (40). Accordingly, we found that nonatopic females had a lower HRQL than males and atopic females.

The main strength of this study is that the level and the determinants of the asthma burden were evaluated in an international framework and that general population samples of adult asthmatic subjects, encompassing a wide spectrum of disease severity (rather than clinically selected groups), were considered. Moreover, the data were collected through a highly standardized protocol (10), which ensures the comparability of the information among the countries involved in the study.

A few caveats should be taken into account when interpreting our results. In this study, the burden was only attributed to asthma, even if we cannot exclude that it could have been caused by other coexisting respiratory conditions, such as COPD, flue or rhinitis,

and it was defined in terms of cost components to the patient and society (i.e. productivity losses, leisure time forgone, hospital services utilization). Unfortunately, the impact on the subjects' productivity was not entirely measured, as no information was collected on daily work performance (i.e., productivity losses that did not result in lost working days). Moreover, the burden of the disease was analysed as a three-level variable to disentangle the asthmatic subjects with a high reduction in daily activities and/or hospital services utilization, from those with only a few reduced activity days. The choice of the cut-offs used to define high productivity losses/leisure time forgone was subjective. However, our definition of burden was negatively associated with the subjects' HRQL for both the physical and mental components of the SF-36 questionnaire. This result supports the construct validity of our outcome, as the SF-36 is a standardized, widely used tool (15). In addition, the main results obtained in the multivariate analysis were confirmed considering different cut-offs (data not shown).

A potential self-selection bias could be present as the asthmatic subjects considered in the analysis were singled out among those who participated in both the ECRHS I and II. Furthermore, self-reporting could have influenced the accuracy of our estimates (41), as all the information pertaining to the outcome was collected through an interviewer administered questionnaire. However, the potential measurement error could have mainly been related to productivity losses and leisure time forgone, and it could have influenced our results only to a minor extent. In fact, our study did not involve elderly patients and the recall period considered in the questionnaire was relatively short for crucial events, such as ED visits and hospitalization (12 months), which tend to be recalled with greater accuracy. Furthermore, the information on relevant predictors (BMI, lung function, IgE sensitization) was collected through objective measurements.

In conclusion, an alarming percentage of asthmatic subjects from the general population in Europe reports productivity losses, leisure time forgone or utilization of hospital services. A heavy burden caused by the disease is reported more frequently by asthmatics with obesity, frequent respiratory symptoms, low lung function, coexisting chronic cough or phlegm, and by women without IgE sensitization to common aeroallergens.

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References

1. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;**9**:687–695.
2. Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol* 2001;**107**:3–8.
3. Bateman ED. Measuring asthma control. *Curr Opin Allergy Clin Immunol* 2001;**1**:211–216.
4. Global Initiative for Asthma (GINA) Report. Global Strategy for Asthma Management and Prevention. Revised 2006. <http://www.ginasthma.com>
5. Bateman ED, Bousquet HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;**170**:836–844.
6. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;**16**:802–807.
7. de Marco R, Bugiani M, Cazzoletti L, Carosso A, Accordini S, Buriani O et al. The control of asthma in Italy. A multicentre descriptive study on young adults with doctor diagnosed current asthma. *Allergy* 2003;**58**: 221–228.
8. Lai CK, De Guia TS, Kim YY, Kuo SH, Mukhopadhyay A, Soriano JB et al. Asthma control in the Asia-Pacific region: the Asthma Insights and Reality in Asia-Pacific Study. *J Allergy Clin Immunol* 2003;**111**:263–268.
9. de Marco R, Cazzoletti L, Cerveri I, Corsico A, Bugiani M, Accordini S et al. Are the asthma guideline goals achieved in daily practice? A population-based study on treatment adequacy and the control of asthma. *Int Arch Allergy Immunol* 2005;**138**:225–234.
10. European Community Respiratory Health Survey II Steering Committee. The European Community Respiratory Health Survey II. *Eur Respir J* 2002;**20**:1071–1079.
11. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;**7**:954–960.
12. American Thoracic Society. Standardization of spirometry, 1994 Update. *Am J Respir Crit Care Med* 1995;**152**:1107–1136.
13. Sunyer J, Zock JP, Kromhout H, Garcia-Esteban R, Radon K, Jarvis D et al. Lung function decline, chronic bronchitis, and occupational exposures in young adults. *Am J Respir Crit Care Med* 2005;**172**:1139–1145.
14. 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 Resp J Suppl* 1993;**16**:5–40.
15. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–483.
16. Ware JE Jr, Snow KK, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center, 1993.
17. Ware JE Jr, Kosinski M, Keller SD. SF-36 physical and mental health summary scales: a user's manual. Boston: Health Assessment Lab, New England Medical Center, 1994.
18. Global Initiative for Asthma (GINA) Report. Global strategy for asthma management and prevention. Update 2002. NIH publication 02-3659.
19. Goldstein H. Multilevel statistical models, 3rd edn. London: Edward Arnold, 2003.
20. Cerveri I, Zoia MC, Bugiani M, Corsico A, Carosso A, Piccioni P et al. Inadequate antiasthma drug use in the north of Italy. *Eur Respir J* 1997;**10**:2761–2765.
21. Janson C, Chinn S, Jarvis D, Burney P. Physician-diagnosed asthma and drug utilization in the European Community Respiratory Health Survey. *Eur Respir J* 1997;**10**:1795–1802.
22. Cerveri I, Locatelli F, Zoia MC, Corsico A, Accordini S, de Marco R. International variations in asthma treatment compliance: the results of the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1999;**14**:288–294.
23. Vermeire PA, Rabe KF, Soriano JB, Maier WC. Asthma control and differences in management practices across seven European countries. *Respir Med* 2002;**96**:142–149.
24. Janson C, de Marco R, Accordini S, Almar E, Bugiani M, Carolei A et al. Changes in the use of anti-asthmatic medication in an international cohort. *Eur Respir J* 2005;**26**:1047–1055.
25. Bateman ED, Frith LF, Braunstein GL. Achieving guideline-based asthma control: does the patient benefit? *Eur Respir J* 2002;**20**:588–595.
26. Anis AH, Lynd LD, Wang XH, King G, Spinelli JJ, Fitzgerald M et al. Double trouble: impact of inappropriate use of asthma medication on the use of health care resources. *CMAJ* 2001;**164**: 625–631.
27. Accordini S, Bugiani M, Arossa W, Gerzeli S, Marinoni A, Olivieri M et al. Poor control increases the economic cost of asthma. A multicentre population-based study. *Int Arch Allergy Immunol* 2006;**141**:189–198.
28. Cockcroft DW, Swystun VA. Asthma control versus asthma severity. *J Allergy Clin Immunol* 1996;**98**(6 Pt 1):1016–1018.
29. Stahl E. Correlation between objective measures of airway calibre and clinical symptoms in asthma: a systematic review of clinical studies. *Respir Med* 2000;**94**:735–741.
30. de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M et al. Prognostic factors of asthma severity: a 9-year international prospective cohort study. *J Allergy Clin Immunol* 2006;**117**:1249–1256.
31. de Marco R, Accordini S, Cerveri I, Corsico A, Antó JM, Künzli N et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *Am J Respir Crit Care Med* 2007;**175**:32–39.
32. Buist AS. Similarities and differences between asthma and chronic obstructive pulmonary disease: treatment and early outcomes. *Eur Respir J Suppl* 2003;**39**:30s–35s.
33. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med* 2006;**100**: 648–657.
34. King GG, Brown NJ, Diba C, Thorpe CW, Munoz P, Marks GB et al. The effects of body weight on airway calibre. *Eur Respir J* 2005;**25**:896–901.
35. Shore SA, Fredberg JJ. Obesity, smooth muscle, and airway hyperresponsiveness. *J Allergy Clin Immunol* 2005;**115**: 925–927.
36. Romanet-Manent S, Charpin D, Magnan A, Lanteaume A, Vervloet D; EGEA Cooperative Group. Allergic vs nonallergic asthma: what makes the difference? *Allergy* 2002;**57**:607–613.

37. de Marco R, Locatelli F, Cerveri I, Bugiani M, Marinoni A, Giammanco G. Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy. *J Allergy Clin Immunol* 2002;**110**:228–235.
38. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J* 2000;**16**:432–436.
39. Boschetto P, Miotto D, Mapp CE. Women and asthma. *Eur Respir Mon* 2003;**25**:90–102.
40. 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**: 611–617.
41. Evans C, Crawford B. Patient self-reports in pharmaco-economic studies. Their use and impact on study validity. *Pharmacoeconomics* 1999;**15**:241–256.

Appendix

Co-ordinating Centre. Project Leader: P. Burney; Statistician: S. Chinn; Principal Investigator: D. Jarvis; Project Co-ordinator: J. Knox; Principal Investigator: C. Luczynska; Assistant Statistician: J. Potts; Data Manager: S. Arinze.

Steering Committee for the ECRHS II. U. Ackermann-Liebrich (University of Basel, Basel, Switzerland); J.M. Antó (Institut Municipal d'Investigació Mèdica (IMIM-IMAS), Universitat Pompeu Fabra (UPF), Barcelona, Spain); P. Burney (Imperial College, London, UK); I. Cerveri (University of Pavia, Pavia, Italy); S. Chinn (King's College London, London, UK); R. de Marco (University of Verona, Verona, Italy); T. Gislason (Landspítali University Hospital, Reykjavik, Iceland); J. Heinrich (GSF – Institute of Epidemiology, Munich, Germany); C. Janson (Uppsala University, Uppsala, Sweden); D. Jarvis (Imperial College); J. Knox (King's College London); N. Künzli (University of Southern California, Los Angeles, USA); B. Leynaert (Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France); C. Luczynska (King's College London); F. Neukirch (INSERM); J. Schouten (University of Groningen, Groningen, The Netherlands); J. Sunyer (IMIM-IMAS, UPF); C. Svanes (University of Bergen, Bergen, Norway); P. Vermeire (University of Antwerp, Antwerp, Belgium); M. Wjst (GSF – Institute of Epidemiology).

List of Principal Investigators and Senior Scientific Team. Belgium: South Antwerp & Antwerp City (P. Vermeire, 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. Björnsson, D. Gislason, T. Blöndal, A. Karlsdóttir). Italy: Turin (M. Bugiani, P. Piccioni, E. Caria, A. Carosso, W. Arossa, C. Romano, D. Fabbro, R. Bono, E. Migliore, G. Castiglioni), Verona (R. de Marco, G. Verlato, E. Zanolini, S. Accordini, A. Poli, V. Lo Cascio, M. Ferrari), Pavia (A. Marinoni, S. Villani, M. Ponzio, A. Carolei, M. Comelli, M. Grassi, I. Cerveri, A. Corsico). The Netherlands: Groningen & Geleen (J. Schouten, M. Kerkhof). 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. Norbäck, M. Gunnbjörnsdóttir), Göteborg (K. Torén, L. Lillienberg, A.C. Olin, B. Balder, A. Pfeifer-Nilsson, R. Sundberg), Umea (E. Norrman, M. Söderberg, K. Franklin, B. Lundbäck, B. Forsberg, L. Nyström). 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).

Centres taking part at their own expense. Australia: Melbourne (M. Abramson, R. Woods, E.H. Walters, F. Thien). France: Bordeaux (A. Taytard, C. Raherison), Montpellier (J. Bousquet, P. Demoly). Germany: Hamburg (K. Richter). USA: Portland (M. Osborne, S. Buist, W. Vollmer, L. Johnson).