# **Original Paper**



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# The Cost of Persistent Asthma in Europe: An International Population-Based Study in Adults

Simone Accordini<sup>a</sup> Angelo G. Corsico<sup>b</sup> Marco Braggion<sup>a</sup> Margaret W. Gerbase<sup>d</sup> David Gislason<sup>e</sup> Amund Gulsvik<sup>f</sup> Joachim Heinrich<sup>g</sup> Christer Janson<sup>h</sup> Deborah Jarvis<sup>i</sup> Rain Jõgi<sup>j</sup> Isabelle Pin<sup>k, I, m</sup> Yvonne Schoefer<sup>g</sup> Massimiliano Bugiani<sup>c</sup> Lucia Cazzoletti<sup>a</sup> Isa Cerveri<sup>b</sup> Alessandro Marcon<sup>a</sup> Roberto de Marco<sup>a</sup> Therapy and Health Economics Working Group of the European Community Respiratory Health Survey II

<sup>a</sup>Unit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, <sup>b</sup>Division of Respiratory Diseases, IRCCS 'San Matteo' Hospital Foundation, University of Pavia, Pavia, and <sup>c</sup>Territorial Unit of Pneumology B, Local Health Agency Turin 2, Turin, Italy; <sup>d</sup>Division of Pulmonary Medicine, University Hospitals of Geneva, Geneva, Switzerland; <sup>e</sup>Department of Allergy, Respiratory Medicine and Sleep, Landspitali University Hospital, Reykjavik, Iceland; <sup>f</sup>Department of Thoracic Medicine, Haukeland University Hospital and Institute of Medicine, University of Bergen, Bergen, Norway; <sup>g</sup>Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; <sup>h</sup>Department of Medical Sciences: Respiratory Medicine & Allergology, Uppsala University, Uppsala, Sweden; <sup>i</sup>Respiratory Epidemiology and Public Health Group, National Heart and Lung Institute, Imperial College, London, UK; <sup>j</sup>Lung Clinic, Tartu University Hospital, Tartu, Estonia; <sup>k</sup>Pédiatrie, Centre Hospitalier Universitaire de Grenoble, <sup>I</sup>INSERM U823, Institut Albert Bonniot, and <sup>m</sup>Université Joseph Fourier, Grenoble, France

## **Key Words**

Asthma · Cost of illness · Disease control

### **Abstract**

**Background:** This study is aimed at providing a real-world evaluation of the economic cost of persistent asthma among European adults according to the degree of disease control [as defined by the 2006 Global Initiative for Asthma (GINA) guidelines]. **Methods:** A prevalence-based cost-of-illness study was carried out on 462 patients aged 30–54 years with persistent asthma (according to the 2002 GINA definition), who were identified in general population samples from 11 European countries and examined in clinical settings in the European Community Respiratory Health Survey II between 1999 and 2002. The cost estimates were computed from the societal perspective following the bottom-up approach on

the basis of rates, wages and prices in 2004 (obtained at the national level from official sources), and were then converted to the 2010 values. Results: The mean total cost per patient was EUR 1,583 and was largely driven by indirect costs (i.e. lost working days and days with limited, not work-related activities 62.5%). The expected total cost in the population aged 30–54 years of the 11 European countries was EUR 4.3 billion (EUR 19.3 billion when extended to the whole European population aged from 15 to 64 years). The mean total cost per patient ranged from EUR 509 (controlled asthma) to EUR 2,281 (uncontrolled disease). Chronic cough or phlegm and having a high BMI significantly increased the individual total cost. **Conclusions:** Among European adults, the cost of persistent asthma drastically increases as disease control decreases. Therefore, substantial cost savings could be obtained through the proper management of adult patients in Europe. Copyright © 2012 S. Karger AG, Basel

### Introduction

In recent years, literature on the socioeconomic burden of asthma [1, 2] and its relationship with the degree of disease control [3, 4] has multiplied in industrialized countries, pointing out that the cost of the disease is considerable both in terms of direct medical expenditures (DMEs) and indirect nonmedical costs (INMCs) [5].

The cost-of-illness (COI) analysis [6] is a useful tool for quantifying the economic burden of a disease and for planning cost containment policies, given that the information is collected at the subject level (bottom-up approach [7]) from representative samples of patients. However, many COI studies on asthma derived their estimates from official statistics (top-down approach [7]) or from clinically selected samples [2], which do not encompass the whole spectrum of disease severity and control.

International population-based COI studies provide updated cost estimates that should be used as a valid metric for comparing with the figures obtained in other countries. However, very few COI analyses on asthma have been carried out at an international level in the general population in Europe [8–10].

The analysis of the economic impact of persistent asthma deserves particular attention, since severe asthmatic subjects bear the most significant burden in terms of high total costs [2], poor quality of life [11] and a high risk of mortality [12]. Therefore, for an optimal allocation of resources and for the improvement of patient healthcare, it is essential to evaluate the cost of the disease for this category of patients. Accordingly, the aim of this study was to provide a real-world evaluation of the economic cost of persistent asthma among adults in Europe and to assess how the cost varies according to the degree of disease control. To achieve these goals, the data from the repeat of the European Community Respiratory Health Survey (ECRHS II) [13] were used.

# **Material and Methods**

Study Design

A prevalence-based COI study [7], i.e. a cross-sectional evaluation of the economic impact of the disease in a year, regardless of the date of onset, was carried out among the 30- to 54-year-old subjects identified in the ECRHS II in Europe as having current asthma.

The ECRHS II was a follow-up study of all the subjects who had been previously investigated in the ECRHS I (stage 2) [14]. The ECRHS I was a multicenter cross-sectional survey on respiratory health carried out between 1991 and 1993 on random samples of young adults (aged 20–44 years) from the general population. Each participant was sent a brief screening 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) were invited to undergo an extended clinical interview and clinical tests (stage 2). The ECRHS II was carried out between 1999 and 2002 (full protocol available at http://www.ecrhs.org). Ethical approval was obtained for each center from the appropriate ethics committee and written consent was obtained from each participant.

Only the 462 individuals with persistent asthma from 11 European countries (Belgium, Estonia, France, Germany, Iceland, Italy, Norway, Spain, Sweden, Switzerland and the UK) were included in the COI analysis (table E1 in suppl. material; for all online suppl.material, seewww.karger.com/doi/10.1159/000338998). Asthma was considered present if a subject had reported physician-diagnosed current asthma [4] at the clinical interview, and the degree of severity was assessed on the basis of the frequency of symptoms, lung function and daily medication regimen, according to the 2002 Global Initiative for Asthma (GINA) guidelines [15, 16]. Persistent asthmatics were further classified according to the 2006 GINA definition of disease control [17, 18]. The definitions used are reported in the supplementary material.

During the clinical interview, all asthmatic subjects provided detailed information about their DMEs [doctor visits, laboratory tests, pharmacological treatment, emergency department (ED) visits and nights spent in hospital] and INMCs (lost working days and days with limited, not work-related activities, such as looking after children, housework or studying) due to breathing problems in the past 12 months. The number of doses of each drug consumed (except oral steroids) was collected for the previous 3-month period and was multiplied by 4 on the assumption that drug consumption in the past 3 months was representative of the entire year. The information on oral steroids was collected for the previous 12-month period.

The economic evaluation was carried out from the societal perspective [19]. The cost components were estimated following the bottom-up approach [7], by multiplying the number of times each patient resorted to healthcare services, the number of doses of each drug consumed, the number of lost working days and the number of days with limited, not work-related activities reported by each subject, by proper monetary unit values (table 1). The monetary unit values were calculated in Euro on the basis of rates, wages and prices in 2004 obtained at the national level from official sources (listed in the suppl. material). Due to the variability of the monetary figures among the ECRHS countries and to the differences among their health systems, the monetary unit value of each cost component was computed as the median of the national figures. When the national monetary values were not available for the reference year, they were converted to the 2004 figures using the corresponding Harmonized Indices of Consumer Prices (HICPs) as annual average inflation rates (Eurostat, http://epp. eurostat.ec.europa.eu).

Statistical Analysis

The mean annual cost per patient [with the 95% confidence interval (CI)] was provided for each cost component. Confidence limits were computed by the bias-corrected and accelerated bootstrap method [21] considering 20,000 replications. The mean total cost per patient was obtained by summing up the estimates of all the cost components, in order to minimize information losses due to miss-

**Table 1.** Monetary unit value of each cost component (reference year: 2004)

Cost component	Monetary unit value <sup>1</sup> (EUR)
Doctor visits	33.69 (general practitioner, chest physician, allergy/internal medicine specialist or ENT doctor)
Clinical and laboratory tests	30.01 (spirometry) 23.24 (skin test for allergy) 109.10 (blood test for allergy-specific IgE) 21.32 (chest X-rays)
Pharmacological treatment	market price of a single dose of each active principle <sup>2</sup>
ED visits	100.19
Hospital admissions (nights spent in hospital)	369.86 (general ward) 390.67 (chest medicine) 822.53 (intensive care unit)
Productivity losses (working days lost)	132.26 <sup>3</sup> 44.45 (housewives) <sup>4</sup>
Leisure time forgone (days with limited, not work-related activities)	26.67 <sup>5</sup>
ENT = Ear, nose and throat. <sup>1</sup> Median of the values from Estonia, France, Germany, Iceland, Italy, Norway, Sweden, Switzerland and the UK (sources used in each country are listed in suppl. material).	<sup>3</sup> Average daily wage (earnings were assumed to reflect productivity according to the human capital approach) [20]. <sup>4</sup> Hourly wage of part-time help (EUR 8.89), 5 working hours per day assumed.

ing individual data. The confidence limits of the mean total cost were derived from the 2.5 and 97.5 percentiles of the distribution of the 20,000 values obtained by summing up the bootstrap estimates of all the cost components in each replication. The expected total cost of persistent asthma was obtained for the population aged 30–54 years of the 11 ECRHS countries in 2004, and was then extended to the 15- to 64-year-old population of the ECRHS countries and of the whole of Europe (see table 3 and suppl. material for the detailed description of these computations). The mean total cost per patient (and its components) and the expected total cost were converted to the 2010 values using the HICPs of the years 2005–10 for

<sup>2</sup> Obtained by averaging the market price of a single dose of the

most prescribed medicines.

A multivariable analysis of the association among the individual total cost (computed as the sum of the available cost components for each subject, rounded to the nearest integer), the degree of disease control and other potential determinants (listed in table 4) was performed by a negative binomial regression model [22] with adjusted standard errors for intracenter correlation. The results were summarized as mutually adjusted ratios of expected individual total costs (REC), which are fitted as incidence rate ratios in the negative binomial regression model.

the Euro area (cost in 2010 = cost in 2004  $\times$  1.1226; Eurostat).

The statistical analysis was performed using STATA software, release 10.1 (StataCorp, College Station, Tex., USA).

### Results

Characteristics of the Subjects with Persistent Asthma according to the Degree of Disease Control

<sup>5</sup> Hourly wage of part-time help (EUR 8.89) as replacement

value, 3 h of limited, not work-related activities per day assumed.

The 462 subjects included in the analysis had mild (22.3%), moderate (34.0%) or severe (43.7%) persistent asthma. The disease was considered controlled, partly controlled or uncontrolled in 6.9, 37.9 and 55.2% of the patients, respectively (table E2 in suppl. material). Thirtynine percent of the subjects with uncontrolled asthma reported chronic cough or phlegm, and more than 50% of them were overweight or obese. The subjects with controlled asthma were more often nonsmokers (59.4%), had a later onset of the disease (65.6% of them reported their first symptoms at the age of 20 or later) and showed a higher percentage of atopic individuals (72.4%) than partly controlled and uncontrolled patients.

The Cost of Persistent Asthma in Europe

The estimated mean total cost per adult patient was EUR 1,583 (95% CI: 1,265–1,942) when converted to the 2010 values (table 2). DMEs represented 37.5% of the total

**Table 2.** Components of the mean total cost per patient with persistent asthma

DMEs	Number of users <sup>1</sup>	Mean number of interventions <sup>2</sup> per user	Mean number of interventions per patient	Mean annual cost per patient in 2004 [95% CI] EUR	Mean annual cost per patient converted to the 2010 values <sup>3</sup> [95% CI] EUR
Doctor visits	263 (57.0%)	4.5	2.5	86 [71–114]	97 [80–128]
General practitioner	210 (45.7%)	4.0	1.8		[ ]
Specialist	117 (25.4%)	2.9	0.7		
Clinical and laboratory tests	111 (24.1%)	3.2	0.8	30 [24–39]	34 [27-44]
Spirometry	97 (21.0%)	1.9	0.4		
Skin tests for allergy	32 (6.9%)	1.2	0.1		
Blood tests for allergy	37 (8.0%)	1.4	0.1		
Chest X-rays	48 (10.4%)	1.6	0.2		
Pharmacological treatment	$401 (86.8\%)^4$	_	_	281 [249-318]	315 [280-357]
ED visits	54 (11.8%)	2.1	0.2	24 [17-39]	27 [19–44]
Nights spent in hospital	17 (3.7%)	7.4	0.3	108 [43–329]	121 [48–369]
INMCs	Number of patients who lost days <sup>5</sup>	Mean number of days per patient who lost days	Mean number of days per patient	Mean annual cost per patient in 2004 [95% CI] EUR	Mean annual cost per patient converted to the 2010 values <sup>3</sup> [95% CI] EUR
Working days lost Days with limited, not	97 (21.7%)	25.7	5.6	594 [399–944]	667 [448–1,060]
work-related activities	85 (18.4%)	58.3	10.8	287 [204-420]	322 [229–471]
Total cost				1,410 [1,127-1,730]	1,583 [1,265–1,942]

<sup>&</sup>lt;sup>1</sup> Users: patients who reported at least one intervention due to breathing problems in the past 12 months.

cost generated by the disease, whereas the remaining 62.5% was due to INMCs. More than half (53.1%) of the DMEs were due to pharmacological treatment, whereas 25.0% were due to the utilization of hospital services. About half (52.1%) of the drug costs derived from the use of inhaled corticosteroids (alone or combined with beta-2-agonists), whereas 27.0 and 9.8% of them derived from the use of inhaled long-acting and short-acting beta-2-agonists, respectively (table E3 in suppl. material).

The expected total cost of persistent asthma in the population aged 30–54 years of the 11 ECRHS countries was EUR 4.3 billion (in the 2010 values). The expected total cost of the disease increased from EUR 4.3 to 7.9 billion when it was extended to the 15- to 64-year-old population

of the ECRHS countries and to EUR 19.3 billion when it was extended to all the European nations (table 3).

The Cost of Persistent Asthma according to the Degree of Disease Control

The mean total cost per patient (in the 2010 values) increased as the degree of disease control decreased, ranging from EUR 509 (95% CI: 366–675) and EUR 702 (95% CI: 412–1,112) among controlled and partly controlled asthmatic subjects, respectively, to EUR 2,281 (95% CI: 1,702–2,983) among uncontrolled patients (fig. 1). A similar pattern was found for doctor visits and clinical/laboratory tests and for INMCs, whereas the mean annual cost per patient due to pharmacological treatment was EUR 446,

<sup>&</sup>lt;sup>2</sup> Interventions: doctor visits, clinical/laboratory tests, pharmacological treatment, emergency department visits, nights spent in hospital.

<sup>&</sup>lt;sup>3</sup> Obtained by multiplying the mean annual cost per patient in 2004 by 1.1226 (HICPs of the years 2005–10 for the Euro area; source: Eurostat).

<sup>&</sup>lt;sup>4</sup> Number of patients who used inhaled drugs (steroids, long-acting beta-2-agonists, short-acting beta-2-agonists, cromogly-cate/nedocromil and antimuscarinic) or oral drugs (antileukotrienes, beta-2-agonists, methylxanthines and ketotifen) in the past 3 months or who used oral steroids in the past 12 months, and who reported the number of doses of each drug consumed.

<sup>&</sup>lt;sup>5</sup> Patients who lost days: patients who lost at least 1 working day or had at least 1 day with limited, not work-related activities because of breathing problems in the past 12 months.

**Table 3.** Expected total cost of persistent asthma in the population aged 15–64 years in Europe

	Number of subjects present on January 1, 2004 <sup>3</sup> (million)	Expected number of cases in 2004 <sup>4</sup> (million)	Expected total cost in 2004 <sup>5</sup> (EUR, billion)	Expected total cost/ GDP <sup>6</sup> in 2004	Expected total cost converted to the 2010 values <sup>8</sup> (EUR, billion)
ECRHS countries <sup>1</sup>	225	5.0	7.0	0.08%	7.9
Other European countries <sup>2</sup>	328	7.2	10.2	$0.33\%^{7}$	11.4
Europe	553	12.2	17.2	0.14%	19.3

GDP = Gross domestic product.

<sup>1</sup> 11 countries (Belgium, Estonia, France, Germany, Iceland, Italy, Norway, Spain, Sweden, Switzerland and the UK).

<sup>2</sup> Thirty-four member states of the Council of Europe on September 1, 2004 (Albania, Andorra, Armenia, Austria, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Finland, Georgia, Greece, Hungary, Ireland, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Moldova, The Netherlands, Poland, Portugal, Romania, Russian Federation, San Marino, Serbia and Montenegro, Slovak Republic, Slovenia, 'The former Yugoslav Republic of Macedonia', Turkey, and Ukraine) and a nonmember state (Belarus).

<sup>3</sup> Source: Eurostat and Council of Europe [23].

<sup>4</sup> Obtained by multiplying the number of subjects present on January 1, 2004 by the prevalence of persistent asthma (2.2%); the latter was derived by multiplying the prevalence of physician-di-

agnosed current asthma (5.6%, estimated from the ECRHS I data) by the proportion of patients with persistent asthma (39.3%, estimated from the ECRHS II data [16]) in the random sample.

<sup>5</sup> Obtained by multiplying the expected number of cases of persistent asthma by the mean total cost per patient (EUR 1,410) in 2004.

<sup>6</sup> Source: International Monetary Fund, World Economic Outlook Database April 2011 (http://www.imf.org); GDPs in US dollars converted to the values in Euro using the average currency exchange rate in 2004 of USD 1 = EUR 0.8039 (source: Bank of Italy, http://uif.bancaditalia.it).

<sup>7</sup> The GDPs of Andorra, Liechtenstein and San Marino were not available.

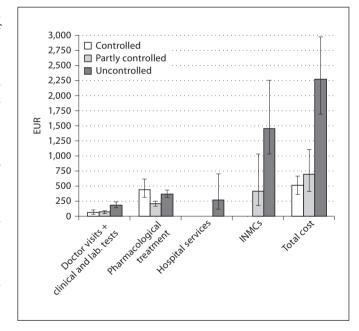
<sup>8</sup> Obtained by multiplying the expected total cost in 2004 by 1.1226 (HICPs of the years 2005–10 for the Euro area; source: Eurostat)

EUR 211 and EUR 370 among controlled, partly controlled and uncontrolled subjects, respectively. The distribution of the cost components differed according to the level of disease control: drug costs accounted for 87.6, 30.1 and 16.2% of the total cost among controlled, partly controlled and uncontrolled patients, respectively, whereas indirect and hospital costs represented 64.1 and 11.8% of the individual burden among uncontrolled subjects (fig. 2).

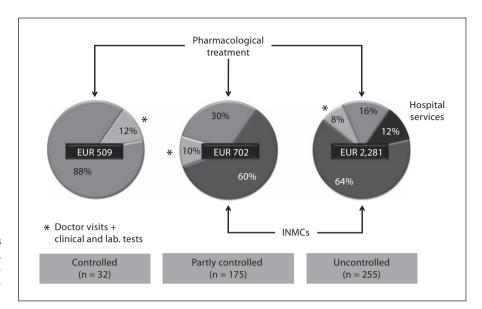
The lack of disease control was the strongest determinant of the individual total cost, which was 3-fold higher among uncontrolled subjects compared to controlled/partly controlled individuals (REC = 3.02, 95% CI: 2.06– 4.44) after adjusting for the effect of the other potential predictors (table 4).

Other Determinants of the Cost of Persistent Asthma

The coexistence of chronic cough or phlegm more than doubled the individual total cost (REC = 2.22, 95% CI: 1.52–3.25) (table 4). Having a high BMI significantly increased the individual total cost (1 unit increase: REC = 1.03, 95% CI: 1.00–1.05), whereas the opposite was observed for immunoglobulin E (IgE) sensitization, the presence of which was associated with a reduction of one third of the individual total cost with respect to



**Fig. 1.** Mean total cost per patient with persistent asthma (in the 2010 values) according to the degree of disease control. Bars represent 95% CIs.



**Fig. 2.** Distribution of the cost components according to the degree of disease control. The mean total cost per patient with persistent asthma (in the 2010 values) is reported.

**Table 4.** Mutually adjusted ratios of expected individual total costs (RECs)<sup>1</sup> due to breathing problems in the past 12 months

	REC (95% CI)	p value
Uncontrolled vs. controlled/	2.02 (2.06, 4.44)	0.001
partly controlled asthma	3.02 (2.06–4.44)	< 0.001
Female	1.37 (0.97–1.94)	0.07
Age (5-year increase)	1.05 (0.91-1.21)	0.51
BMI (1-unit increase)	1.03 (1.00-1.05)	0.03
Low socioeconomic class <sup>2</sup>	0.81 (0.53-1.24)	0.34
Smoking habits <sup>3</sup> , vs. nonsmoker		
Past smoker	1.02 (0.67-1.56)	0.93
Current smoker	0.74 (0.46-1.19)	0.22
Age at onset, vs. 0–9 years		
10-19 years	0.88 (0.66-1.18)	0.40
≥20 years	0.90 (0.59-1.36)	0.61
Chronic cough or phlegm <sup>4</sup>	2.22 (1.52-3.25)	< 0.001
Allergic rhinitis <sup>5</sup>	0.89(0.54-1.46)	0.65
IgE sensitization <sup>6</sup>	0.63 (0.39–1.00)	0.051

<sup>&</sup>lt;sup>1</sup> Obtained by using a negative binomial regression model with adjusted standard errors for intracenter correlation.

among 4 environmental allergens (Dermatophagoides pteronyssinus, cat, Timothy grass and Cladosporium herbarum).

nonatopic subjects (REC = 0.63, 95% CI: 0.39-1.00), even if this association did not reach the statistical significance.

### Discussion

To our knowledge, this study is the first COI analysis on both DMEs and INMCs of persistent asthma among adult patients in Europe, who were randomly selected from the general population and evaluated in clinical settings. Economic research on persistent asthmatics is seminal, because even though they do not constitute the majority of asthmatic subjects, they do consume a large proportion of healthcare funding devoted to the disease [24].

Our main findings are: (1) the economic cost of persistent asthma was high among adults in Europe and it was largely driven by INMCs, (2) the failure to control symptoms was the major determinant of the individual total cost and (3) coexisting chronic cough or phlegm and a high BMI significantly increased the individual total cost.

# The Cost of Persistent Asthma in Europe

The expected total cost of persistent asthma was high in the adult population in Europe. This result highlights the fact that the total cost of asthma is probably higher than previously reported for the whole population in Europe (EUR 17.7 billion per annum) [24], since our figure refers only to adult patients with a persistent degree of

<sup>&</sup>lt;sup>2</sup> Having completed full-time education before the age of 16.

<sup>&</sup>lt;sup>3</sup> Subjects were considered smokers – current or past – if they had reported having smoked at least 20 packs of cigarettes or 360 g of tobacco in their lifetime, or at least 1 cigarette/day or 1 cigar/week for 1 year.

<sup>&</sup>lt;sup>4</sup> Having reported cough and/or phlegm from the chest, usually in winter and on most days for as long as 3 months each year.

 <sup>&</sup>lt;sup>5</sup> Having reported any nasal allergies including hay fever.
 <sup>6</sup> Having at least one specific IgE measurement ≥ 0.35 kU/l

severity and some cost components were not measured. However, our estimate should be interpreted with caution since it was based on the strong assumption that, in the population aged from 15 to 64 years, different European countries had the same mean annual cost per patient and the same prevalence of persistent asthma.

INMCs exceeded DMEs, in agreement with the results reported in a recent systematic review [2], in which indirect costs ranged from 52 (Italy) [25] to 75% (Germany) [26] of the total cost in Europe. However, the comparability of cost estimates among COI studies could be limited because of differences in health systems, definition of costs, data sources, reference populations or time periods.

Pharmacological treatment was the main cost-driver of DMEs. This result is consistent with estimates from other COI studies in Europe [2], in which medications ranged from 45 (Spain) [27] to 84% (Germany) [26] of direct costs. Drug expenditure was largely due to inhaled corticosteroids, since these medications are considered the first-line therapy for asthma by the GINA guidelines [28], with a consequent increase in their use between 1990 and 2000 [29].

The Cost of Persistent Asthma Was Four-Fold Higher among Uncontrolled Patients

Poor control of symptoms was the main determinant of the cost of persistent asthma among adults in Europe, and this positive association was confirmed after adjusting for a set of potential predictors. Our result is consistent with the findings of previous COI studies in different countries [2, 10], in which poor asthma control was associated with an increase in healthcare and elevated costs.

We used the composite measure of disease control proposed by the 2006 GINA guidelines [17], as it combines several markers of uncontrolled asthma (diurnal and nocturnal symptoms, limitation of activities, the need for reliever or rescue treatment, lung function and exacerbations), which should be considered together to define the global health status of patients [30]. A previous analysis of the ECRHS II data, in which this measure was used, showed that a majority of current asthmatics were poorly controlled in 2000 [18]. Furthermore, according to the Asthma Control Test score, the proportion of patients in Europe whose asthma is not well-controlled had not improved between 2006 and 2008 [31]. Therefore, substantial cost savings for both the society and individuals could be obtained by the proper management of patients, which could be achieved through national asthma plans [32], since the savings in the cost

of uncontrolled asthma far outweigh the additional cost of the control measures [33]. Accordingly, having found that the utilization of hospital services and INMCs accounted for 71.8% of the total cost, the amount of the expected total cost that could be avoided in the European population aged 15–64 years was impressive (EUR 13.9 billion).

Other Determinants of the Cost of Persistent Asthma

Coexisting chronic cough or phlegm increased the cost of persistent asthma. A positive relationship with both INMCs and high DMEs was already found among adult patients from the general population in Italy [3]. Higher costs are incurred by asthmatic patients with this symptom because they could have a poorer level of disease control [34] and/or a more severe form of asthma [35]. Accordingly, we found that the patients with chronic cough or phlegm had reported a lack of disease control and had had severe persistent asthma more frequently than the subjects without this symptom. Alternatively, those with chronic cough or phlegm could be the most difficult patients to treat due to the coexistence of asthma and chronic obstructive pulmonary disease (COPD) [36]. In fact, chronic cough or phlegm significantly increases the risk of developing COPD in adult subjects, regardless of smoking habits [37].

A high BMI was significantly associated with a higher individual total cost. In a previous analysis of the ECRHS II data on all current asthmatics [4] and in agreement with other studies [38], we found that obese asthmatics reported a heavier socioeconomic burden than nonobese patients, regardless of respiratory symptoms and lung function. Obese subjects may have behavioral difficulties regarding the self-management of asthma and diet, and may have mechanical limitations due to decreased lung volume and reduced airway caliber [39, 40].

The individual total cost was higher among asthmatics without IgE sensitization compared to atopic patients (even if this association did not reach the statistical significance). This can be justified by the fact that nonatopic asthma in adults is often more severe than atopic asthma [41]. Accordingly, we found that the patients without IgE sensitization had a later onset and a higher frequency of chronic cough or phlegm than atopic individuals, both of which are associated with a poor prognosis [35, 42].

Strengths and Weaknesses of the Study

The main strength of this analysis is that DMEs and INMCs of persistent asthma were estimated at an international level in several European countries, and that

general population samples of asthmatic subjects (encompassing the whole spectrum of disease control) were considered rather than clinically selected groups. Moreover, the data were collected through a highly standardized protocol [13], which ensured the comparability of the information among centers.

A few caveats should be taken into account when interpreting our results. The cost estimates were only attributed to persistent asthma, even if we cannot exclude that they could have been due to other coexisting respiratory conditions. The cost of the disease was partially underestimated since some cost components were not valued due to lack of data. In particular, we did not consider premature mortality due to asthma, which is not negligible [43, 44] even in this age class [24], because we performed a cross-sectional evaluation of the costs incurred by patients in the previous year. No or incomplete information was collected on direct nonmedical costs, on the adverse impact of asthma on daily work performance and on premature retirement due to the disease [45]. In addition, we could not evaluate the influence of comorbidities on asthma costs [46].

A potential self-selection bias could have been present since the asthmatic subjects considered in the analysis were singled out among those who participated in both the surveys (ECRHS I and II) [18]. Furthermore, self-reporting could have influenced the accuracy of our estimates [47], as part of the information was collected through an interviewer-administered questionnaire and

the recall period considered (12 months) could have been too long for some cost components [48], such as productivity losses and leisure time forgone.

Finally, some circumstances that could influence the cost estimates have changed since the collection of the ECRHS II data. In particular, the GINA guidelines should have a greater influence on the way patients are treated nowadays than they were 10 years ago.

### **Conclusions**

The economic cost of persistent asthma is high among adult patients from the general population in Europe and increases drastically with the lack of disease control. Therefore, substantial cost savings for both the society and individuals could be obtained through the proper management of adult patients in Europe.

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