The Impact of Cigarette Smoking on Asthma: A Population-Based International Cohort Study

Isa Cerveri^a Lucia Cazzoletti^b Angelo G. Corsico^a Alessandro Marcon^b
Rosanna Niniano^a Amelia Grosso^a Vanessa Ronzoni^a Simone Accordini^b
Christer Janson^c Isabelle Pin^{d,e} Valerie Siroux^{d,f} Roberto de Marco^b

^aDivision of Respiratory Diseases, IRCCS San Matteo Hospital Foundation, University of Pavia, Pavia, ^bUnit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, Italy; ^cDepartment of Medical Sciences, Respiratory Medicine and Allergology, University of Uppsala, Uppsala, Sweden; ^dUnit 823, National Institute of Health and Medical Research (INSERM), ^eGrenoble Teaching Hospital, and ^fUniversité Joseph Fourier-Grenoble 1, Grenoble, France

Key Words

Asthma • Cigarette smoking • Epidemiology

Abstract

Background: The prevalence rates of smoking in subjects with asthma have frequently been reported as similar to those in the general population; however, available data are not up-to-date. There is only limited and somewhat conflicting information on the long-term effects of smoking on health outcomes among population-based cohorts of subjects with asthma. We aimed to investigate changes in smoking habits and their effects on forced expiratory volume in 1 s (FEV₁) in subjects with asthma in comparison with the rest of the population, focusing on the healthy smoker effect.

Methods: We studied 9,092 subjects without asthma and 1,045 with asthma at baseline who participated in both the European Community Respiratory Health Survey I (20–44 years old in 1991–1993) and II (1999–2002). **Results:** At follow-up, smoking was significantly less frequent among subjects with asthma than in the rest of the population (26 vs. 31%; $p < 0.001$). Subjects with asthma who were already ex-smok-

ers at the beginning of the follow-up in the 1990s had the highest mean asthma score (number of reported asthma-like symptoms, range 0–5), probably as a result of the healthy smoker effect (2.80 vs. 2.44 in never smokers, 2.19 in quitters and 2.24 in smokers; $p < 0.001$). The influence of smoking on FEV₁ decline did not depend on asthma status. Smokers had the highest proportion of subjects with chronic cough/phlegm ($p < 0.01$). **Conclusion:** One out of 4 subjects with asthma continues smoking and reports significantly more chronic cough and phlegm than never smokers and ex-smokers. This stresses the importance of smoking cessation in all patients with asthma, even in those with less severe asthma.

Copyright © 2012 S. Karger AG, Basel

Introduction

Many recent papers have reported that cigarette smoking is surprisingly frequent in asthma patients, with a prevalence that is relatively close to that found in the general population [1–4]. However, smoking has been great-

ly reduced in the last 20 years in the developed countries [5], and available data on the prevalence of cigarette smoking in subjects with and without asthma are not up-to-date.

Cigarette smoking and asthma can be a dangerous mix, but there are only limited published data on the long-term effects of smoking on symptoms, lung function, response to asthma treatment and health care utilization among population-based cohorts of subjects with asthma. The most important longitudinal surveys specifically addressing this topic showed additive or even multiplicative effects of smoking and asthma on the decline in forced expiratory volume in 1 s (FEV₁) [6–8]. These surveys were conducted between the 1970s and 1990s, when smoking was more common than it is nowadays, and it is expected that the association between asthma and smoking has been modified these past decades because of clinical recommendations [9].

In the more recent, large, international, population-based cohort of subjects with asthma followed up for 9 years in the European Community Respiratory Health Survey (ECRHS), a somewhat surprising lack of association between smoking and lung function decline was found. This aroused the speculation that this finding could reflect, at least in part, the healthy smoker effect, i.e. only subjects with asthma with fewer symptoms and/or preserved lung function smoke or continue smoking [10, 11], whereas subjects with more severe asthma refrain from smoking. The healthy smoker effect could also explain the lack of association between cigarette smoke and the risk of developing asthma found in some recent papers [12–14].

Thus, we specifically reanalysed the 9-year follow-up data from the ECRHS to evaluate changes in smoking habits and their effects on lung function decline in subjects with asthma in comparison with the rest of the population, focusing on the healthy smoker effect.

Methods

Study Design

The ECRHS is an international multicentre study of respiratory health. The first survey (ECRHS I) [15] was carried out from 1991 to 1993 on random community-based samples of adults aged 20–44 years. Each participant was sent a brief questionnaire (stage 1), and from those who responded, a random sample of 20% was invited to undergo a more detailed clinical examination (stage 2). In addition, a sample consisting of subjects from stage 1 not already included in the random sample who reported asthma-like symptoms in the last 12 months or who were using asthma medication was also studied. The ECRHS II was a follow-up study

of all the participants in stage 2 of the ECRHS I, performed between 1998 and 2002 (the full protocol can be found at <http://www.ecrhs.org>) [16]. In both studies, subjects answered a standardized questionnaire administered by trained interviewers, and they underwent lung function and blood tests. Ethical approval was obtained for each centre from the appropriate institutional or regional ethics committee, and written consent was obtained from each participant.

Subjects and Definitions

In the analysis of the longitudinal data, we considered all the subjects identified in stage 2 of ECRHS I who participated in ECRHS II ($n = 17,480$). Four hundred and eighty-six subjects with past (but not current) diagnosed asthma at the ECRHS I or with missing information on self-reported asthma, asthma-like symptoms or medication utilization in the last 12 months were excluded from this analysis. In the end, 15,293 subjects without asthma and 1,701 subjects with diagnosed current asthma were considered. Out of the subjects with asthma, 1,045 (61.4%) participated in ECRHS II (1998–2002), and out of the subjects without asthma, 9,092 (59.4%) participated (p value for the difference = 0.114).

Diagnosis of Asthma

Asthma was defined by the report of asthma confirmed by a doctor and respiratory symptoms (wheeze, nocturnal chest tightness, attack of breathlessness following activity, at rest or at night-time, at least one asthma attack) or utilization of asthma medications in the previous 12 months [11]. The change in asthma status over the 2 surveys was also classified as follows: no asthma (subjects who did not report current asthma, either at ECRHS I or ECRHS II), remittent asthma (subjects who reported current asthma at ECRHS I but not at ECRHS II), incident asthma (subjects who did not report current asthma at ECRHS I but reported current asthma at ECRHS II) and persistent asthma (subjects who reported current asthma both at ECRHS I and ECRHS II).

Smoking Habits at ECRHS I and II and Pattern of Change in Smoking Habits

In both surveys, subjects were classified according to their smoking habits as never smokers, ex-smokers or current smokers (at least one cigarette per day in the past month). To describe the change in smoking habits, subjects were classified as follows: (1) never smokers, (2) ex-smokers (ex-smoker both at ECRHS I and II, or non-smoker at ECRHS I and ex-smoker at ECRHS II), (3) quitters (current smoker at ECRHS I and ex-smoker at ECRHS II) and (4) smokers [17].

Smoking Intensity and Equivalences

The mean daily number of cigarettes in smokers and the mean number of lifetime pack-years in smokers and ex-smokers were calculated.

Cigarillos were considered equivalent to 3 cigarettes, and cigars to 5; pipe tobacco was converted to equivalence by weight [18].

Lung Function

The maximum FEV₁ and forced vital capacity of at least 2 and as many as 5 technically acceptable maneuvers were recorded, according to the American Thoracic Society (ATS) criteria for reproducibility [19].

At ECRHS I, lung function was missing for 2,110 subjects without diagnosed current asthma (13.8%), and it was not measured in compliance with the ATS criteria for 516 subjects without asthma (3.4%). The same figures in subjects with asthma were 181 (10.6%) and 59 (3.5%), respectively.

At the ECRHS II, lung function was missing for 1,513 subjects without diagnosed current asthma (17.5%) and was not measured in compliance with the ATS criteria or was considered unreliable due to the utilization of inhaled long-acting β_2 -agonists in the 12 h before the test for 244 subjects without asthma (2.8%). The same figures in subjects with asthma were 216 (15.9%) and 84 (6.2%), respectively.

Airflow obstruction was defined as FEV₁/forced vital capacity less than the lower limit of normal at the first (ECRHS I) and second visit (ECRHS II) [20].

Bronchial Responsiveness

Subjects were considered to have hyperresponsiveness on the methacholine bronchial provocation test if the provocative dose of methacholine causing a 20% fall in FEV₁ was <1 mg [21]. At ECRHS I, among subjects without asthma, the methacholine challenge test was not performed in 90 subjects (0.6%) due to exclusion criteria and in 4,366 subjects (28.6%) due to other reasons. The same figures in subjects with asthma were 108 (6.4%) and 540 (31.8%), respectively.

Chronic Cough/Phlegm

Subjects with asthma were considered to have chronic cough/phlegm if they reported to have had cough or phlegm on most days for a minimum of 3 months a year and for at least 2 successive years.

Allergen Sensitization

At baseline (ECRHS I), specific IgE antibodies 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.

Asthma Score

The asthma score used in the analyses was derived from Sunyer et al. [22] and consisted of a simple count of the positive answers to 5 questions on the ECRHS I and ECRHS II questionnaires; i.e. the score ranges from 0 to 5. The items were as follows: (1) breathless when wheezing and wheezing apart from cold at any time in the last 12 months; (2) woken up with a feeling of chest tightness in the last 12 months; (3) attack of shortness of breath at rest in the last 12 months; (4) attack of shortness of breath after exercise in the last 12 months, and (5) woken by attack of shortness of breath in the last 12 months [22].

Statistics

Data are summarized as percentages, or means with standard deviation. Percentages and means were adjusted for sex, age, height and body mass index (BMI) by means of 2-level (with level-1 units, subjects, nested into level-2 units, centres) random-intercept multiple linear, Poisson or logistic regression models. The χ^2 test and the Wilcoxon test were used to test differences, as appropriate ($\alpha = 0.05$).

The association between the pattern of change in smoking habits and FEV₁ decline was assessed by a 2-level random-intercept multiple linear regression model fitted on subjects participating in both surveys. Age and BMI at ECRHS I, sex, height and change in asthma status between the 2 surveys were included in the model as covariates. The interactions between the pattern of change in smoking habits and change in asthma status between the 2 surveys and between the pattern of change in smoking habits and sex were also assessed using the Wald test.

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

Results

Comparison of Participants and Non-Participants in the Follow-Up

Of the 17,480 subjects participating in the ECRHS I from 28 centres, 10,296 participated in ECRHS II (response rate 59%), and the average follow-up time was 8.9 years (range 5.8–11.7 years). The median number of participants across centres was 586.5 (range 310–1,252). The participation rate in the ECRHS II was lower among those who were smokers at ECRHS I (54.4%) than among ex-smokers (60.9%) or never smokers (62.2%; $p < 0.001$).

Change in Smoking Habits from ECRHS I to ECRHS II

Smoking habits were significantly different between subjects with and without asthma at ECRHS I ($p < 0.05$). Among subjects without asthma, 43% were never smokers, 18% ex-smokers, 10% quitters and 30% smokers. The corresponding figures for subjects with asthma were 48, 18, 8 and 26%, respectively. At the ECRHS I, the mean daily number of cigarettes smoked was significantly lower in subjects with asthma than in subjects without asthma (14.7 ± 9.7 vs. 15.9 ± 10.4 ; $p = 0.007$). The change in smoking habits between the 2 surveys was fairly similar in subjects with and without asthma; the proportion of never smokers was stable, the proportion of smokers decreased and the proportion of ex-smokers increased (fig. 1). The mean variation in the mean daily number of cigarettes in smokers was not significantly different in the 2 groups. Smoking habits were also significantly different between subjects with and without allergen sensitization at ECRHS I ($p < 0.0001$), with the proportion of never smokers being greater in subjects with allergen sensitization than in subjects without, and the percentage of smokers being greater in subjects without allergen sensitization than in subjects with. When considering gender differences, among men at the ECRHS I, 41% were never smokers, 22% ex-smokers and 37% smokers; the corre-

Table 1. Pattern of smoking habits at ECRHS II according to gender and asthma and allergen sensitization at ECRHS I

		Never smokers %	Ex-smokers %	Quitters %	Smokers %	p value
Gender	men (n = 4,397)	39.4	18.7	10.5	31.4	<0.0001
	women (n = 4,776)	46.8	16.8	8.3	28.1	
Asthma at ECRHS I	no (n = 8,224)	42.7	17.7	9.5	30.1	0.0175
	yes (n = 949)	47.6	18.1	8.0	26.3	
Allergen sensitization at ECRHS I	no (n = 5,497)	41.3	18.2	10.0	30.5	<0.0001
	yes (n = 2,815)	47.5	17.2	8.5	26.9	

All values adjusted for height and gender, as well as for age, asthma and BMI at ECRHS I. Numbers of subjects shown in parentheses only include those subjects who had no missing values for the considered variables (height and gender, as well as age, asthma, allergen sensitization and BMI at ECRHS I).

Fig. 1. Percentage of never smokers, ex-smokers and smokers at ECRHS I and ECRHS II according to current asthma status at ECRHS I. Percentages of never smokers, ex-smokers and smokers at ECRHS II were determined by adding the net change observed in subjects participating in both surveys to baseline percentages [calculated on the basis of all subjects with information on smoking habits participating in ECRHS I (n = 15,259 and n = 1,696 for subjects without and with asthma at ECRHS I, respectively)].

sponding figures for females were 48, 20 and 32%, respectively. The change in smoking habits during the follow-up was more evident among males than females and was even more evident when considering ex-smokers and quitters together (29% in males vs. 25% in females); this resulted in a similar percentage of smokers at the end of follow-up (table 1).

Longitudinal Association between Smoking and Symptoms and Lung Function

After adjusting for age and BMI at ECRHS I, height and sex among subjects with asthma, the mean symptom score at ECRHS I was significantly different for never smokers, ex-smokers, quitters and smokers ($p = 0.0084$; table 2). In particular, those who were already ex-smokers at ECRHS I and remained ex-smokers at ECRHS II had

the highest mean symptom score at ECRHS I. Smokers had the highest proportion of subjects with chronic cough/phlegm at ECRHS I (p for the difference among groups = 0.0497). No significant difference in baseline lung function and bronchial hyperresponsiveness according to the pattern of change in smoking habits was found, even though the percentage of subjects with bronchial hyperresponsiveness among smokers with asthma was lower than that among the other groups (table 2). The only interaction between gender and smoking habit was found for FEV_1 ($p = 0.015$), which was 93% of predicted in males and 102% of predicted in females among ex-smokers; male ex-smokers in particular had the lowest FEV_1 at ECRHS I.

After adjusting for age and BMI at ECRHS I, height and sex, FEV_1 decline was similar in the 872 subjects with

Table 2. Baseline clinical and functional status of the subjects with asthma at ECRHS I according to the pattern of change in smoking habits during the follow-up

	Never smokers (n = 508)	Ex-smokers (n = 178)	Quitters (n = 76)	Smokers (n = 264)	p
Symptom score	2.44 ± 0.23	2.80 ± 0.26	2.19 ± 0.23	2.24 ± 0.21	0.0084
Chronic cough/phlegm, %	42.1	42.5	48.4	51.7	0.0497
FEV ₁ /FVC, %	78.4 ± 0.8	78.9 ± 1.0	78.0 ± 1.3	77.9 ± 0.9	0.7412
FEV ₁ , % predicted	97.3 ± 1.0	97.7 ± 1.5	97.6 ± 2.0	96.8 ± 1.2	0.9532
Airflow obstruction, %	20.5	19.0	23.3	21.9	0.7713
Bronchial hyperresponsiveness, %	64.7	63.6	58.8	53.6	0.1555

Values represent means ± SD where appropriate. All values adjusted for sex, as well as for age, height and BMI at ECRHS I.

Table 3. Mean FEV₁ at baseline and mean FEV₁ decline according to the change in asthma status and change in smoking habits between ECRHS I and II, and multiple regression coefficients for the association between FEV₁ decline, change in asthma status and change in smoking habits between ECRHS I and II

	FEV ₁ at baseline ml	Mean FEV ₁ decline ml/year	Regression coefficient for FEV ₁ decline
Change in asthma status			
No asthma	3.76 (3.72, 3.79)	29.0 (25.9, 32.0)	0
Remittent asthma	3.65 (3.57, 3.73)	32.1 (26.3, 37.8)	3.1 (−1.9, 8.1)
Incident asthma	3.56 (3.50, 3.61)	32.2 (28.0, 36.4)	−3.2 (0.2, 6.3)*
Persistent asthma	3.38 (3.33, 3.42)	27.1 (23.3, 30.9)	−1.9 (−4.4, 0.6)
Change in smoking habits			
Never smokers	3.73 (3.70, 3.77)	28.3 (25.2, 31.5)	0
Ex-smokers	3.74 (3.70, 3.78)	25.9 (22.5, 29.3)	−2.4 (−4.4, −0.4)*
Quitters	3.70 (3.65, 3.74)	25.8 (22.0, 29.5)	−2.6 (−5.1, −0.1)*
Smokers	3.67 (3.63, 3.70)	33.1 (29.9, 36.3)	−4.8 (3.1, 6.5)*

All values adjusted for age and BMI at ECRHS I, as well as for sex and height. Values in parentheses represent 95% CIs. * Statistically significant at the 5% level.

persistent asthma, in the 183 subjects with remittent asthma and in the 8,457 subjects who did not report current asthma either in the ECRHS I or ECRHS II. In contrast, the 534 subjects with incident asthma showed a greater decline in FEV₁ than subjects who did not report current asthma either in the ECRHS I or ECRHS II. Considering together subjects with and without asthma, the FEV₁ decline was significantly lower in ex-smokers and quitters and greater in smokers in comparison with never smokers (table 3). Allergen sensitization at ECRHS I was not significantly associated with FEV₁ decline. No significant interaction between change in asthma status and change in smoking habits nor between sex and change in smoking habits was found.

Discussion

The most important findings of our study are as follows: (1) smoking is significantly less frequent among subjects with asthma than in the rest of the population; however, 1 out of 4 subjects with asthma continues smoking; (2) subjects with asthma with the highest mean symptom score and, among males, those with the lowest lung function were already ex-smokers at the beginning of the follow-up in the 1990s, and the percentage of subjects with bronchial hyperresponsiveness among smokers with asthma was lower than among the other groups at ECRHS I, which is probably a result of the healthy smoker effect; (3) the influence of smoking on FEV₁ de-

cline is similar for subjects with and without asthma, and (4) smokers with asthma report significantly more chronic cough/phlegm than never smokers and ex-smokers.

The prevalence rates of smoking in subjects with asthma have frequently been reported in the literature as similar to those of the general population [2, 23]. However, more recent cross-sectional results from the large database of the Epidemiological Study on the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness and Atopy study have already documented that subjects with asthma smoke significantly less than subjects without [24]. A prospective epidemiological cardiopulmonary study conducted in a sample of the Copenhagen population from 1976 to 2004 showed that the prevalence of smokers among subjects with asthma declined significantly over the study period from approximately 60% to approximately 30% [25]. Our European data collected at the beginning of 2000 confirm this trend, setting the percentage of smokers among subjects with and without asthma at 26 and 31%, respectively.

Many papers have speculated on the selection bias in asthma termed the healthy smoker effect but, at least to our knowledge, it has never been demonstrated [26]. The healthy smoker effect has been suggested as one of the possible explanations of the lack of a statistical relationship between current smoking and asthma risk [27, 28]. Our present analysis considers the changes in smoking habits during follow-up with respect to the previous studies in the ECRHS. Thus, we could specifically document that this important selection factor can explain the attenuation of the detrimental effect of smoking in subjects with asthma and in subjects with allergen sensitization. Subjects with asthma with the highest mean symptom score and, among males, those with the lowest lung function were already ex-smokers at the beginning of our follow-up in the early 1990s, probably as a result of the healthy smoker effect. This may also explain the low percentage of smokers with asthma with bronchial hyperresponsiveness even at ECRHS I and the lower FEV₁ decline in ex-smokers and quitters compared to never smokers; only subjects with asthma with relatively good lung function at baseline smoke or start smoking, whereas subjects with more severe asthma traits refrain from smoking. Although it could be expected that women take better care of their health and therefore the healthy smoker effect could be stronger in women than in men, our findings do not support this hypothesis, in line with the findings of Norbäck et al. [29]. The relatively young age of our subjects and the relatively low exposure to active smoking could also play a role in explaining the absence of an in-

teraction between asthma and smoking with regard to the decline in lung function. Interestingly, we found an effect of asthma on FEV₁ decline only when considering subjects with incident asthma during the follow-up; probably, beside the relatively young age of our subjects, the possible explanation of this finding is that subjects with persistent asthma already had lower lung function at the beginning of the follow-up compared to those with remittent and incident asthma.

Our smokers with asthma had the highest proportion of subjects with chronic cough/phlegm. A strong association between mucus hypersecretion and smoking in young subjects with asthma was already found in the Copenhagen City Heart Study [25]. Chronic cough/phlegm is probably accepted as a natural consequence of smoking by subjects with asthma as well as by normal subjects and is thus not sufficient to induce subjects to give up smoking. Even if in epidemiology up to one third of smokers over the age of 50 years with an asthma diagnosis may in fact have chronic obstructive pulmonary disease, we believe that the problem of misclassification in our analysis would be limited by the young age of our sample (20–44 years) and by the use of the self-reported doctor diagnosis of asthma to identify our subjects.

A strength of our study is the large, international, population-based cohort of subjects with asthma followed up for 9 years and the detailed characterization of the changes in smoking habits during the entire follow-up. The somewhat conflicting results reported in the literature on the impact of smoking on asthma may be explained by the fact that patients recruited in clinics generally have a more severe form of asthma, and therefore they do not represent all the several phenotypes of the disease that can be found in the general population. The authors of one of the most recent studies state that, to generalize the findings, there is need of a larger population of subjects with asthma with different grades of severity [30].

A limitation of our study is the relatively low rate of response to the ECRHS II and the higher drop-out rate of smokers than never smokers or ex-smokers in the longitudinal analysis. However, the ECRHS response rate is similar to that obtained in many other long-term surveys. The overall response rate in the 20- to 35-year age group of the Copenhagen City Heart Study reported in a recent paper on the prevalence of self-reported asthma in young adults declined from 83.9% in the 1976–1978 survey to 55.1% in the 2001–2004 survey [25].

In conclusion, even if it is encouraging that a large proportion of subjects with asthma reporting more asthma-like symptoms had already quit smoking, 1 out of 4 sub-

jects with asthma continues smoking and reports significantly more chronic cough/phlegm than never smokers and ex-smokers. Besides the relatively young age of our sample and the relatively low exposure to active smoking, the healthy smoker effect could explain the absence of an interaction between asthma and smoking with regard to the decline in lung function. Further efforts should be devoted to encouraging smoking cessation in patients with asthma who continue smoking and to develop strategies for preventing tobacco use in young patients.

Acknowledgments

Coordinating Centre

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

Steering Committee for the ECRHS II

U. Ackermann-Lieblich (University of Basel, Basel, Switzerland); J.M. Antó (Institut Municipal d'Investigació Mèdica and Universitat Pompeu Fabra, 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 (Iceland 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, Calif., USA); B. Leynaert (Institut National de la Santé et de la Recherche Médicale, Paris, France); C. Luczynska (King's College London); F. Neukirch (Institut National de la Santé et de la Recherche Médicale); J. Schouten (University of Groningen, Groningen, The Netherlands); J. Sunyer (Institut Municipal d'Investigació Mèdica and Universitat Pompeu Fabra); 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

P. Vermeire, J. Weyler, M. Van Sprundel, V. Nelen (South Antwerp and Antwerp City, Belgium); E.J. Jensen (Aarhus, Denmark); R. Jogi, A. Soon (Tartu, Estonia); F. Neukirch, B. Leynaert, R. Liard, M. Zureik (Paris, France); I. Pin, J. Ferran-Quentin (Grenoble, France); J. Heinrich, M. Wjst, C. Frye, I. Meyer (Erfurt, Germany); T. Gislason, E. Björnsson, D. Gislason, T. Blöndal, A. Karlsdóttir (Reykjavik, Iceland); M. Bugiani, P. Piccioni, E. Caria, A. Carosso, E. Migliore, G. Castiglioni (Turin, Italy); R. de Marco, G. Verlato, E. Zanolini, S. Accordini, A. Poli, V. Lo Cascio, M. Ferrari (Verona, Italy); A. Marinoni, S. Villani, M. Ponzio, F. Frigerio, M. Comelli, M. Grassi, I. Cerveri, A. Corsico (Pavia, Italy); J. Schouten, M. Kerkhof (Groningen and Geleen, The Netherlands); A. Gulsvik, E. Omenaas, C. Svanes, B. Laerum (Bergen, Norway); J.M. Antó, J. Sunyer, M. Kogevinas, J.P. Zock, X. Basagana, A. Jaen, F. Burgos (Barcelona, Spain); J. Maldonado, A. Pereira, J.L. Sanchez (Huelva, Spain); J. Martinez-Moratalla Rovira, E. Almar

(Albacete, Spain); N. Muniozguren, I. Urritia (Galdakao, Spain); F. Payo (Oviedo, Spain); C. Janson, G. Boman, D. Norbäck, M. Gunnbjörnsdóttir (Uppsala, Sweden); K. Torén, L. Lillienberg, A.C. Olin, B. Balder, A. Pfeifer-Nilsson, R. Sundberg (Göteborg, Sweden); E. Norrman, M. Söderberg, K. Franklin, B. Lundbäck, B. Forsberg, L. Nyström (Umea, Sweden); N. Künzli, B. Dibbert, M. Hazenkamp, M. Brutsche, U. Ackermann-Lieblich (Basel, Switzerland); D. Jarvis, B. Harrison (Norwich, UK); D. Jarvis, R. Hall, D. Seaton (Ipswich, UK).

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, Oreg. (M. Osborne, S. Buist, W. Vollmer, L. Johnson).

Funding

The co-ordination of the ECRHS II was supported by the European Commission as part of their Quality of Life Programme. All funds were used during the collection of data. The study design, the analysis and interpretation of data, the writing of the report and the decision to submit the paper for publication were completely independent of these funds.

The following bodies funded the local studies in ECRHS II included in this paper. Albacete, Spain: Fondo de Investigaciones Sanitarias (grant No. 97/0035-01, 99/0034-01 and 99/0034-02), Hospital Universitario de Albacete, Consejería de Sanidad. Antwerp, Belgium: FWO (Fund for Scientific Research)-Flanders Belgium (grant No. G.0402.00), University of Antwerp, Flemish Health Ministry. Barcelona, Spain: SEPAR, Public Health Service (grant No. R01 HL62633-01), Fondo de Investigaciones Sanitarias (grant No. 97/0035-01, 99/0034-01 and 99/0034-02), CIRIT (grant No. 1999SGR 00241). Basel, Switzerland: Swiss National Science Foundation, Swiss Federal Office for Education & Science, Swiss National Accident Insurance Fund (SUVA). Bergen, Norway: Norwegian Research Council, Norwegian Asthma & Allergy Association, Glaxo Wellcome AS, Norway Research Fund. Bordeaux, France: Institut Pneumologique d'Aquitaine. Erfurt, Germany: GSF – National Research Centre for Environment & Health, Deutsche Forschungsgemeinschaft (grant No. FR 1526/1-1). Galdakao, Spain: Basque Health Department. Göteborg, Sweden: Swedish Heart Lung Foundation, Swedish Foundation for Health Care Sciences & Allergy Research, Swedish Asthma & Allergy Foundation, Swedish Cancer & Allergy Foundation. Grenoble, France: Programme Hospitalier de Recherche Clinique-DRC de Grenoble 2000 (No. 2610), Ministry of Health, Direction de la Recherche Clinique, Ministère de l'Emploi et de la Solidarité, Direction Générale de la Santé, CHU de Grenoble, Comité des Maladies Respiratoires de l'Isère. Hamburg, Germany: GSF – National Research Centre for Environment & Health, Deutsche Forschungsgemeinschaft (grant No. MA 711/4-1). Ipswich and Norwich, UK: Asthma UK (formerly known as National Asthma Campaign). Huelva, Spain: Fondo de Investigaciones Sanitarias (grant No. 97/0035-01, 99/0034-01 and 99/0034-02). Montpellier, France: Programme Hospitalier de Recherche Clinique-DRC de Grenoble 2000 (No. 2610), Ministry of Health, Direction de la Recherche Clinique, CHU de Grenoble, Ministère de l'Emploi et de

la Solidarité, Direction Générale de la Santé, Aventis (France), Direction Régionale des Affaires Sanitaires et Sociales Languedoc-Roussillon. Oviedo, Spain: Fondo de Investigaciones Sanitarias (grant No. 97/0035-01, 99/0034-01 and 99/0034-02). Paris, France: Ministère de l'Emploi et de la Solidarité, Direction Générale de la Santé, UCB-Pharma (France), Aventis (France), Glaxo France, Programme Hospitalier de Recherche Clinique-DRC de Grenoble 2000 (No. 2610), Ministry of Health, Direction de la Recherche Clinique, CHU de Grenoble. Pavia, Italy: GlaxoSmithKline Italy, Italian Ministry of University and Scientific and Technological Research, local university funding for research 1998 and 1999 (Pavia, Italy), Italian Medicines Agency (AIFA) (contract No. FARM5JYS5A). Portland, Oreg., USA: American Lung Association of Oregon, Northwest Health Foundation, Collins Foundation, Merck Pharmaceutical. Reykjavik, Iceland: Icelandic Research Council, Icelandic University Hospital Fund. Tartu, Estonia: Estonian Science Foundation. Turin, Italy: ASL 4 Regione Piemonte (Italy), AO CTO/ICORMA Regione Piemonte (Italy), Ministero dell'Università e della Ricerca Scientifica (Italy), Glaxo Wellcome S.p.A. (Verona, Italy). Umeå, Sweden: Swedish Heart Lung Foundation, Swedish Foundation for Health Care Sciences & Allergy Research, Swedish Asthma & Allergy Foundation, Swedish Cancer & Allergy Foundation. Uppsala, Sweden: Swedish Heart Lung Foundation, Swedish Foundation for Health Care Sciences & Allergy Research, Swedish Asthma & Allergy Founda-

tion, Swedish Cancer & Allergy Foundation. Verona, Italy: University of Verona, Italian Ministry of University and Scientific and Technological Research, GlaxoSmithKline Italy.

The following bodies funded ECRHS I for centres in ECRHS II: Belgian Science Policy Office, National Fund for Scientific Research; Ministère de la Santé, Glaxo France, Institut Pneumologique d'Aquitaine, Contrat de Plan Etat-Région Languedoc-Roussillon, CNMATS, CNMRT (90MR/10, 91AF/6), Ministre délégué de la santé, RNSP, France; GSF, and the Bundesministerium für Forschung und Technologie, Bonn, Germany; Ministero dell'Università e della Ricerca Scientifica e Tecnologica, CNR, Regione Veneto grant RSF No. 381/05.93, Italy; Norwegian Research Council project No. 101422/310; Dutch Ministry of Wellbeing, Public Health and Culture, The Netherlands; Ministerio Sanidad y Consumo Fondo de Investigaciones Sanitarias (grant No. 91/0016060/00E-05E and 93/0393), and grants from the Hospital General de Albacete, Hospital General Juan Ramón Jiménez, Consejería de Sanidad Principado de Asturias, Spain; the Swedish Medical Research Council, the Swedish Heart Lung Foundation, the Swedish Association against Asthma and Allergy; Swiss National Science Foundation grant No. 4026-28099; National Asthma Campaign, British Lung Foundation, Department of Health, South Thames Regional Health Authority, UK; United States Department of Health, Education and Welfare Public Health Service (grant No. 2 S07 RR05521-28).

References

- Boulet LP, Lemièrre C, Archambault F, Carrier G, Descary MC, Deschesnes F: Smoking and asthma: clinical and radiologic features, lung function, and airway inflammation. *Chest* 2006;129:661-668.
- Boulet LP, Dorval E, Labrecque M, Turgeon M, Montague T, Thivierge RL: Towards Excellence in Asthma Management: final report of an eight-year program aimed at reducing care gaps in asthma management in Quebec. *Can Respir J* 2008;15:302-310.
- Thomson NC, Chaudhuri R, Livingston E: Asthma and cigarette smoking. *Eur Respir J* 2004;24:822-833.
- Haughney J, Price D, Kaplan A, Chrystyn H, Horne R, May N, et al: Achieving asthma control in practice: understanding the reasons for poor control. *Respir Med* 2008;102:1681-1693.
- 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.
- 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;339:1194-1200.
- 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;171:109-114.
- Apostol GG, Jacobs DR Jr, Tsai AW, Crow RS, Williams OD, Townsend MC, et al: Early life factors contribute to the decrease in lung function between ages 18 and 40: the Coronary Artery Risk Development in Young Adults study. *Am J Respir Crit Care Med* 2002;166:166-172.
- James AL, Knuiman MW, Divitini ML, Hui J, Hunter M, Palmer LJ, et al: Changes in the prevalence of asthma in adults since 1966: the Busselton health study. *Eur Respir J* 2010;35:273-278.
- 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.
- Marcon A, Corsico A, Cazzoletti L, Bugiani M, Accordini S, Almar E, et al: Body mass index, weight gain, and other determinants of lung function decline in adult asthma. *J Allergy Clin Immunol* 2009;123:1069-1074.
- de Marco R, Locatelli F, Cazzoletti L, Bugiani M, Carosso A, Marinoni A: Incidence of asthma and mortality in a cohort of young adults: a 7-year prospective study. *Respir Res* 2005;16:6-95.
- Torén K, Gislason T, Omenaas E, Jögi R, Forsberg B, Nyström L, et al: A prospective study of asthma incidence and its predictors: the RHINE study. *Eur Respir J* 2004;24:942-946.
- Antó JM, Sunyer J, Basagaña X, Garcia-Esteban R, Cerveri I, de Marco R, et al: Risk factors of new-onset asthma in adults: a population-based international cohort study. *Allergy* 2010;65:1021-1030.
- Burney PG, Luczynska C, Chinn S, Jarvis D: The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954-960.
- European Community Respiratory Health Survey II Steering Committee: The European Community Respiratory Health Survey II. *Eur Respir J* 2002;20:1071-1079.
- 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;27:517-524.
- Lange P, Groth S, Nyboe J, Mortensen J, Appleyard M, Schnohr P, et al: Determinants of chronic mucus hypersecretion in a general population with special reference to the type of tobacco smoked. *Int J Epidemiol* 1989;18:882-887.
- Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107-1136.
- Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al: Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-968.

- 21 Chinn S, Jarvis D, Luczynska CM, Ackermann-Liebrich U, Antó JM, Cerveri I, et al: An increase in bronchial responsiveness is associated with continuing or restarting smoking. *Am J Respir Crit Care Med* 2005; 172:956–961.
- 22 Sunyer J, Pekkanen J, Garcia-Esteban R, Svanes C, Künzli N, Janson C, et al: Asthma score: predictive ability and risk factors. *Allergy* 2007;62:142–148.
- 23 Hylkema MN, Sterk PJ, de Boer WI, Postma DS: Tobacco use in relation to COPD and asthma. *Eur Respir J* 2007;29:438–445.
- 24 Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F: Relationships of active smoking to asthma and asthma severity in the EGEA study. *Eur Respir J* 2000;15:470–477.
- 25 Browatzki A, Ulrik CS, Lange P: Prevalence and severity of self-reported asthma in young adults, 1976–2004. *Eur Respir J* 2009; 34:1046–1051.
- 26 Becklake MR, Lalloo U: The ‘healthy smoker’: a phenomenon of health selection? *Respiration* 1990;57:137–144.
- 27 Eisner MD: Smoking and adult asthma. A healthy smoker effect? *Am J Respir Crit Care Med* 2002;165:1566–1567.
- 28 Basagaña X, Sunyer J, Zock JP, Kogevinas M, Urrutia I, Maldonado JA, et al: Incidence of asthma and its determinants among adults in Spain. *Am J Respir Crit Care Med* 2001; 164:1133–1137.
- 29 Norbäck D, Zock JP, Plana E, Heinrich J, Svanes C, Sunyer J, et al: Lung function decline in relation to mould and dampness in the home: the longitudinal European Community Respiratory Health Survey ECRHS II. *Thorax* 2011;66:396–401.
- 30 Chaudhuri R, McSharry C, McCoard A, Livingston E, Hothersall E, Spears M, et al: Role of symptoms and lung function in determining asthma control in smokers with asthma. *Allergy* 2008;63:132–135.