Long-Term Outcomes in Mild/Moderate Chronic Obstructive Pulmonary Disease in the European Community Respiratory Health Survey

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Rationale: Little is known about the long-term outcomes of individuals with mild/moderate chronic obstructive pulmonary disease (COPD) according to spirometric criteria.

Objectives: To test whether nonsmokers and asymptomatic subjects with a spirometric diagnosis of COPD have a steeper decrease in lung function and higher hospitalization rates than subjects without airway obstruction.

Methods: A total of 5,205 subjects without asthma (20–44 years of age) from the general population, with FEV1 > 50% predicted at baseline, were followed for 9 years in the framework of an international cohort study. Percent decrease in FEV1 (%ΔFEV1) and the annual hospitalization rate for respiratory causes during the follow-up were assessed for each subject.

Measurements and Main Results: At baseline, 324 (6.2%) subjects had the prebronchodilator FEV1/FVC ratio less than the lower limit of normal (LLN-COPD), and 105 (2.0%) subjects had the same ratio less than 0.70 (modified GOLD-COPD). At follow-up, smokers with LLN-COPD (n = 205) had a greater mean %ΔFEV1 (%1.7%; 95% confidence interval [CI], 0.8–2.7) and a higher hospitalization rate (rate ratio [RR], 2.52; 95% CI, 1.65–3.86) than normal subjects. Similarly, symptomatic subjects with LLN-COPD (n = 104) had %ΔFEV1 (%2.0%; 95% CI, 0.8–3.3) and the hospitalization rate (RR, 4.18; 95% CI, 2.43–7.21) higher than the reference group. By contrast, nonsmokers and asymptomatic subjects with LLN-COPD had outcomes that were similar or even better than normal subjects. Among subjects with LLN-COPD, the association of symptoms with %ΔFEV1 varied according to smoking habits (P = 0.007); it was particularly strong in symptomatic smokers and disappeared in asymptomatic nonsmokers. Similar results were found with the modified GOLD classification.

Conclusions: In relatively young populations, COPD is associated with poor long-term outcomes in smokers and in symptomatic subjects only.

Keywords: COPD; cohort studies; spirometry; hospitalization; smoking

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of disability and death (1–3). It is largely underdiagnosed (4) and affects a substantial percentage of young adults (5). The two current definitions of COPD are based exclusively on the presence of airflow obstruction assessed by spirometry (6). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has defined COPD as a postbronchodilator FEV1/FVC ratio < 0.70 (7, 8). Because the FEV1/FVC ratio decreases with age at different sex rates, the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines on lung function testing (9, 10) have proposed using the lower limit of normal (LLN) instead of a fixed cut-off to define COPD.

The evidence in favor of one or the other approach is scanty because few validation and/or longitudinal studies on the risk of adverse outcomes in subjects classified with the two different definitions of COPD have been performed (11). In a recent longitudinal analysis of data from the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) (12), Bridevaux and colleagues found that the presence or absence of respiratory symptoms at baseline was the predictor of the long-term outcomes in subjects with mild COPD (13). In fact, symptomatic subjects classified as COPD at baseline by GOLD criterion had a faster lung function decline, increased respiratory care utilization, and a lower health-related quality of life than asymptomatic subjects with normal lung function. On the

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Little is known about the long-term outcomes of subjects diagnosed as mild/moderate chronic obstructive pulmonary disease according to spirometric criteria.

What This Study Adds to the Field

Young adults without asthma with the same spirometric diagnosis of mild/moderate chronic obstructive pulmonary disease show a different decrease in lung function and different hospitalization rates during the following 9 years, according to smoking habits and respiratory symptoms.
contrary, asymptomatic GOLD-COPD subjects had long-term outcomes similar to those of normal asymptomatic subjects. This finding seems to suggest that other factors, such as symptoms or risk factors, should be taken into account to improve the validity of the diagnosis of subjects with mild COPD.

The aim of this analysis was to test whether spirometric definitions alone are able to predict long-term respiratory outcomes (decrease in lung function and hospitalization for respiratory causes) in subjects without asthma but with mild/moderate COPD who did not report respiratory symptoms or who were nonsmokers at baseline. For this purpose, the data from the European Community Respiratory Health Survey (ECRHS) were analyzed.

Some of the results of this study have been previously reported in the form of an abstract (14).

METHODS

Study Design

The ECRHS I is an international multicenter study on respiratory diseases performed over the period 1991 to 1993 on random samples of adults aged 20 to 44 years (15). Each participant was sent a brief

Table 1. Main characteristics of the subjects without asthma belonging to the European Community Respiratory Health Survey cohort according to the presence of mild/moderate chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th></th>
<th>LLN COPD− (n = 4,881)</th>
<th>COPD+ (n = 324)</th>
<th>Modified GOLD COPD− (n = 5,112)</th>
<th>COPD+ (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>51.5</td>
<td>54.3</td>
<td>51.8</td>
<td>37.1</td>
</tr>
<tr>
<td>Age, yr, mean (SD)</td>
<td>34.1 (7.1)</td>
<td>34.6 (6.9)</td>
<td>34.0 (7.1)</td>
<td>38.6 (5.6)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>23.9 (3.7)</td>
<td>23.9 (4.0)</td>
<td>23.8 (3.7)</td>
<td>24.7 (4.6)</td>
</tr>
<tr>
<td>Low educational level, %</td>
<td>20.7</td>
<td>21.2</td>
<td>20.9</td>
<td>18.1</td>
</tr>
<tr>
<td>Ever-smokers, %</td>
<td>57.3</td>
<td>63.5</td>
<td>57.3</td>
<td>69.5</td>
</tr>
<tr>
<td>Pack-years,* median (IQR)</td>
<td>9.6 (4.2–18.0)</td>
<td>15.0 (7.2–24.5)</td>
<td>9.6 (4.2–18.0)</td>
<td>23.4 (12.0–33.7)</td>
</tr>
<tr>
<td>FEV₁% predicted, mean (SD)</td>
<td>107.6 (12.3)</td>
<td>95.0 (12.2)</td>
<td>107.2 (12.4)</td>
<td>90.1 (13.5)</td>
</tr>
<tr>
<td>50% &lt; FEV₁ &lt; 80% predicted, %</td>
<td>1.4</td>
<td>11.7</td>
<td>1.6</td>
<td>22.9</td>
</tr>
<tr>
<td>Respiratory symptoms, %</td>
<td>24.3</td>
<td>32.7</td>
<td>24.6</td>
<td>35.0</td>
</tr>
<tr>
<td>Chronic cough, %</td>
<td>6.8</td>
<td>11.1</td>
<td>7.1</td>
<td>11.4</td>
</tr>
<tr>
<td>Chronic phlegm, %</td>
<td>5.8</td>
<td>9.3</td>
<td>6.0</td>
<td>6.7</td>
</tr>
<tr>
<td>Dyspnea, %</td>
<td>17.2</td>
<td>22.7</td>
<td>17.3</td>
<td>26.9</td>
</tr>
</tbody>
</table>

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; LLN = lower limit of normal.
* Among ever-smokers.
† Presence of chronic cough or phlegm and/or presence of dyspnea.
SYMPTOMS (CHRONIC COUGH OR PHLEGM AND/OR DYSPNEA) AT BASELINE

THE PRESENCE OF MILD/MODERATE LOWER LIMIT OF NORMAL—CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND RESPIRATORY

adjusted for length of follow-up, sex, age, body mass index, educational level, smoking habits at baseline by a two-level linear regression model.

hospitalization for respiratory causes

Percent decrease in FEV1 (TABLE 2. PERCENT DECREASE IN FEV1 AND HOSPITALIZATION FOR RESPIRATORY CAUSES DURING THE FOLLOW-UP ACCORDING TO THE PRESENCE OF MILD/MODERATE LOWER LIMIT OF NORMAL—CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND RESPIRATORY SYMPTOMS (CHRONIC COUGH OR PHLEGM AND/OR DYSPNEA) AT BASELINE

Subjects

A total of 10,897 participants in the ECRHS I stage 2 from 25 centers in 11 European countries had lung function measurements fulfilling the ATS criterion for reproducibility (17) and did not report a diagnosis of asthma during lifetime at baseline, as defined by positive answers to the questions “Have you ever had asthma?” and “Was this confirmed by a doctor?” (Figure 1). Among these subjects, 5,235 individuals were traced in the ECRHS II and had valid lung function measurements at the second survey without reporting a diagnosis of asthma during the follow-up.

Baseline Measurements

The subjects considered in the analysis were classified according to the presence of airflow obstruction at baseline, defined by a prebronchodilator FEV1/FVC ratio < 0.70 (modified GOLD) or < LLN according to age and sex. The LLN equations for FEV1/FVC were obtained from 2,536 “normal” nonsmokers who participated in the ECRHS I stage 2 (18). The maximum FEV1 and FVC from at least two and up to five technically satisfactory maneuvers were considered. The subjects were further classified according to the presence of respiratory symptoms (chronic cough or phlegm and/or dyspnea) and smoking habits at baseline (see the online supplement for a detailed description of the variables). A set of characteristics measured at baseline were taken into account in the analysis: sex, age, body mass index, and low educational level.

Long-term Outcomes

The functional and clinical outcomes evaluated in the second survey were (1) percent decrease in FEV1 (ΔFEV1,%)) during the follow-up, computed as the difference between the measurements in the ECRHS I and in the ECRHS II, divided by the measurement at baseline (a positive value of ΔFEV1,% indicates a decrease), and (2) hospitalization for respiratory causes, which was considered present if a subject reported at least one emergency department (ED) visit and/or one hospital admission during the follow-up period.

Statistical Analysis

The analysis was performed separately for each criterion (LLN and modified GOLD) by stratifying the subjects according to the presence of spirometrically defined COPD at baseline (mild/moderate COPD vs. “normal”). The only subject who had FEV1 <50% predicted (severe screening questionnaire (stage 1). From those who responded, a random sample and a “symptomatic sample” (made up of the subjects who had reported nocturnal shortness of breath or asthma attacks in the past 12 months or who had reported taking asthma medication in stage 1) were selected to undergo a more detailed clinical examination (stage 2).

The ECRHS II is a follow-up study of the participants in the ECRHS I stage 2, performed between 1999 and 2002, who underwent the same clinical examination as in the first survey (the full protocol is available at www.ecrhs.org) (16). Ethical approval was obtained for each center from the appropriate Ethics Committee, and written consent was obtained from each participant.

Baseline Measurements

The subjects considered in the analysis were classified according to the presence of airflow obstruction at baseline, defined by a prebronchodilator FEV1/FVC ratio < 0.70 (modified GOLD) or < LLN according to age and sex. The LLN equations for FEV1/FVC were obtained from 2,536 “normal” nonsmokers who participated in the ECRHS I stage 2 (18). The maximum FEV1 and FVC from at least two and up to five technically satisfactory maneuvers were considered. The subjects were further classified according to the presence of respiratory symptoms (chronic cough or phlegm and/or dyspnea) and smoking habits at baseline (see the online supplement for a detailed description of the variables). A set of characteristics measured at baseline were taken into account in the analysis: sex, age, body mass index, and low educational level.

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Spirometric Classification and Characteristics of the Subjects at Baseline

Among subjects without asthma, the percentage of mild/moderate COPD defined according to the LLN criterion (LLN-COPD) was 6.2%, which was threefold higher than the percentage of modified GOLD-COPD (2.0%) (Table 1). In this age class, the modified GOLD-COPD group was a subset of the subjects classified as COPD by the LLN criterion. The individuals with LLN-COPD were characterized by a higher percentage of females and a lower mean age than those who met the modified GOLD criterion. Only 11.7 and 22.9% of the subjects without asthma but with LLN- and modified GOLD-COPD had 50% \( \leq \) FEV\(_1\) < 80% predicted (moderate COPD), respectively. The self-reported use of inhaled corticosteroids (at both the surveys or for at least 3 years during the follow-up) was very rare: 2.5 and 4.8% in the LLN and modified GOLD groups, respectively.

Association between Spirometric Classification at Baseline and Long-term Outcomes

The average length of follow-up was 8.9 years. Overall, subjects without asthma but with “spirometrically defined mild/moderate COPD” had worse long-term outcomes than subjects without airflow obstruction (Figure 2). In particular, a stronger mean \( \Delta \)FEV\(_1\)% (9.7 vs. 7.6%) and a higher rate of hospitalization (8.7 vs. 7.8 cases/1,000/yr) for respiratory causes were observed among modified GOLD-COPD than among LLN-COPD subjects during the follow-up. The results obtained by using the LLN criterion (highest number of subjects with COPD) are presented in the text. Results obtained with the modified GOLD criterion can be found in the online supplement.

Association between COPD and Long-term Outcomes According to the Presence of Respiratory Symptoms at Baseline

Symptomatic subjects classified as mild/moderate COPD according to the LLN criterion had statistically significant and worse long-term outcomes than subjects without airflow obstruction (Figure 3). In particular, a stronger mean \( \Delta \)FEV\(_1\)% (9.7 vs. 7.6%) and a higher rate of hospitalization (8.7 vs. 7.8 cases/1,000/yr) for respiratory causes were observed among modified GOLD-COPD than among LLN-COPD subjects during the follow-up. The results did not change when using asymptomatic individuals without airflow obstruction as the reference category (Figure 3). In particular, symptomatic subjects (with or without airflow obstruction) showed a higher and statistically significant rate of respiratory care hospitalization than asymptomatic individuals with normal lung function. Similar results were obtained when using the modified GOLD criterion instead of the LLN classification (see the online supplement).

Association between COPD and Long-term Outcomes According to Smoking Habits at Baseline

Current and past smokers classified as mild/moderate COPD according to the LLN criterion had significantly worse long-term outcomes than normal subjects, whereas nonsmokers with airflow obstruction had similar or even better long-term outcomes than subjects without airflow obstruction (Table 3). The same results were observed when the reference category in-
Interaction between Respiratory Symptoms and Smoking Habits in Subjects with Mild/Moderate COPD

Among subjects with COPD, according to the LLN spirometric criterion, a statistically significant interaction was found between respiratory symptoms, smoking behavior, and the percent decrease in FEV1 (P = 0.007). The FEV1 decrease was particularly strong in symptomatic smokers, whereas asymptomatic nonsmokers had the lowest FEV1 decrease (Figure 5). No interaction was found between symptoms, smoking behavior, and the rate of hospitalization for respiratory causes.

The percentage of asymptomatic nonsmokers among subjects with LLN-COPD was 29.0%. This group of subjects had longitudinal outcomes that were similar or even better than subjects with normal lung function (crude mean ΔFEV1%; 6.4 vs. 6.5%, P = 0.997; crude hospitalization rate for respiratory causes: 2.4 vs. 3.4 cases/1,000/yr, P = 0.56). Similar results were found in subjects with COPD according to the modified GOLD criterion (see the online supplement).

Sensitivity Analyses

The previous results were confirmed when the comparisons of the long-term outcomes among the groups were also adjusted for the self-reported use of inhaled corticosteroids, when the subjects with COPD with 50% ≤ FEV1 < 80% predicted (moderate COPD) were excluded from the analysis, when smoking was evaluated at the end of follow-up, and when current smoking at baseline was considered instead of ever smoking (data not shown). In the latter case, the association between smoking behavior and health outcomes in COPD was even stronger. The results were also confirmed when the centers with a response rate lower than the first quartile (43.9%) were excluded from the analysis.

DISCUSSION

The need for longitudinal studies to evaluate the prognostic value of different COPD definitions has been widely acknowledged (8, 20). However, until a short time ago, only two published longitudinal studies were available (18, 21), which compared one criterion with the other and reached contrasting results. Moreover, in both the studies, the role that symptoms or risk factors had in predicting the long-term outcomes was not considered.

In the most recent longitudinal analysis of the data from the SAPALDIA study, Briveaux and colleagues concluded that the presence of respiratory symptoms was of major importance in predicting long-term clinical outcomes in subjects with COPD with mild obstruction (13). This conclusion was based upon the evidence that a large percentage of asymptomatic subjects diagnosed as having COPD by spirometric criteria did not experience clinically relevant events.

Association between Spirometric Diagnosis of COPD and Long-term Outcomes

In the present analysis, we used the data of the 9-year ECRHS follow-up of young adults to evaluate the role that symptoms and smoking habits have in predicting the main clinical outcomes in subjects with mild/moderate airflow obstruction. Our findings document that “spirometrically defined COPD” was associated with a steeper lung function decrease and a higher rate of hospitalization for respiratory causes. However, smoking behavior and, to a minor extent, respiratory symptoms were the actual predictors of the longitudinal outcomes. In fact, (1) nonsmokers and/or asymptomatic subjects with spirometrically defined COPD experienced a decrease in FEV1 and had a hospitalization rate for respiratory causes similar to normal subjects; (2) an interaction between smoking behavior, symptoms, and a decrease in FEV1 was found among subjects with airflow obstruction (symptoms were associated with a faster loss of lung function only in smokers); and (3) asymptomatic nonsmokers represented about 25% of COPD subjects and had long-term outcomes similar to or even better than subjects without airflow obstruction.

The results were the same when using the LLN or the modified GOLD-COPD definition. They suggest that in young adults without asthma, a definition of mild/moderate COPD that is based only on spirometric measures captures a variety of different conditions, ranging from those that may represent a pathologic response to exogenous or endogenous agents to those that may represent a normal variant of lung function, with little potential of developing a clinical disease. In fact, a substantial percentage of subjects (asymptomatic nonsmokers),

| TABLE 3. PERCENT DECREASE IN FEV1 AND HOSPITALIZATION FOR RESPIRATORY CAUSES DURING THE FOLLOW-UP ACCORDING TO THE PRESENCE OF MILD/MODERATE LOWER LIMIT OF NORMAL–CHRONIC OBSTRUCTIVE PULMONARY DISEASE SMOKING HABITS AT BASELINE |
|-------------------------------------------------------------|-------------------------------------------------------------|
| **Percent decrease in FEV1 (ΔFEV1,%)**                      | **ΔFEV1,%**                                                 |
| Subjects, n                                                 | Crude mean, % (95% CI)                                     |
| Nonsmokers        | 4,881                                                     |
| Ever-smokers      | 4,861                                                     |
| Adjusted beta regression coefficient^1, % (95% CI)          | 6.5 (6.4 to 6.7)                                            |
| Hospitalization for respiratory causes                      | 0.0                                                        |
| Subjects, n                                                 | 118                                                       |
| Nonsmokers        | 2,881                                                     |
| Ever-smokers      | 2,861                                                     |
| Adjusted rate ratio (95% CI)                                 | 3.4 (2.9 to 4.0)                                            |
|                   | 1.00                                                       |

*P < 0.001.

^1 All subjects with normal lung function, regardless of smoking habits and respiratory symptoms.

^2 Difference between the mean ΔFEV1% among ever- or nonsmokers with COPD and the mean ΔFEV1% in the reference category (COPD−), adjusted for length of follow-up, sex, age, body mass index, educational level, and respiratory symptoms at baseline by a two-level linear regression model.

^3 Adjusted for sex, age, body mass index, educational level, and respiratory symptoms at baseline by a two-level Poisson regression model with robust standard errors (obtained through the Huber/White/sandwich estimator of the variance).
ranging from 23.3% (modified GOLD) to 29.0% (LLN), had a 9-year lung function decline and a history of hospitalization for respiratory causes that was similar to normal subjects, even if they were classified as COPD by spirometry. As a consequence, our findings support the view of those clinical investigators who, having recognized the heterogeneity of the ‘‘spirometrically defined COPD’’ phenotype, have tried to develop alternative classification systems (not based exclusively on lung function measurements) to define more homogeneous groups (22, 23). Furthermore, our findings suggest that, at least in epidemiological research, smoking habits and the presence of respiratory symptoms should integrate the spirometric definition of mild/moderate COPD, if one wants the COPD label to identify subjects with a worse long-term prognosis.

Decrease in Lung Function

COPD is characterized by an accelerated decline in lung function (24). Consequently, FEV\textsubscript{1} (and its change over time) is one of the most important outcomes in COPD. FEV\textsubscript{1} decline has been recognized as an indicator of disease progression (25) and it is predictive of morbidity, mortality, and hospitalization rates (26). In our study, the steeper FEV\textsubscript{1} decline in mild/moderate COPD was due to the subgroups of smokers and symptomatic subjects.

Figure 4. Adjusted beta regression coefficients (top) and adjusted hospitalization rate ratios (bottom) for respiratory causes according to the presence of mild/moderate lower limit of normal–COPD and smoking habits at baseline among the subjects without asthma identified in the European Community Respiratory Health Survey (ECRHS) I and traced in the ECRHS II. Reference category: nonsmokers with normal lung function. Difference between the mean ∆FEV\textsubscript{1},% in each group and the mean ∆FEV\textsubscript{1},% in the reference category adjusted for length of follow-up, sex, age, body mass index (BMI), educational level, and respiratory symptoms at baseline by a two-level linear regression model (top). Adjusted for sex, age, BMI, educational level, and respiratory symptoms at baseline by a two-level Poisson regression model with robust standard errors (obtained through the Huber/White/sandwich estimator of the variance) (bottom).

Cigarette smoking is the most well-known risk factor for poor respiratory health in adults (27). More than 30 years ago, Fletcher and Peto reported in their seminal work (24) that FEV\textsubscript{1} decline was significantly enhanced in a subgroup of smokers (‘‘susceptible smokers’’) who developed a clinically significant airflow obstruction, whereas most smokers lost FEV\textsubscript{1} as slowly as nonsmokers. In our international cohort of young adults, smokers with airflow obstruction at baseline experienced a faster lung function decrease, whereas smokers with a normal FEV\textsubscript{1}/FVC at baseline showed a similar rate of decline to nonsmokers. This finding confirms that the effect of smoking leads to structural changes (airflow obstruction) only in susceptible subjects who undergo a rapid loss of lung function.

Several studies reported that the presence of respiratory symptoms is a prognostic marker of a faster loss of lung function in normal subjects (28, 29) and in subjects with COPD. However, our study found that in subjects with airflow obstruction, symptoms were associated with lung function decline only among smokers, suggesting that young symptomatic smokers with mild/moderate airflow obstruction represent a high-risk subgroup.

The interaction of symptoms and smoking habits on the progression of COPD, although confirmed even considering changes in smoking behavior or after adjusting for use of inhaled corticosteroids during the follow-up (data not shown), deserves further investigation.
Hospitalization for Respiratory Causes

Hospitalization for respiratory causes is another specific and relevant outcome for COPD. In fact, patients with COPD may suffer recurrent exacerbations, which are associated with an impaired quality of life, reduced survival, and a high rate of hospitalizations (30, 31).

In agreement with previous evidence (32, 33), we found that smoking habits and symptoms strongly and independently increased the risk of hospitalization for respiratory causes in subjects with COPD. As in the case of FEV₁ decrease, asymptomatic nonsmokers with a spirometric diagnosis of COPD had similar or even lower rates of hospitalization than normal subjects, confirming that these subjects are likely to be false-positive cases of COPD.

Comparison between LLN and Modified GOLD Criteria

Although the aim of this study was not to compare the two current classification criteria of COPD, our findings give some insight into their performance in young adults. The modified GOLD and the LLN are associated with long-term outcomes and have a similar rate of false positives. Neither of them predicts outcomes in nonsmokers and asymptomatic subjects with airflow obstruction. Furthermore, the fact that the modified GOLD criterion identifies a smaller number of young adults and is more strongly associated with the two studied outcomes than the LLN criterion highlights that the former has a higher specificity and a lower sensitivity than the latter and vice versa. This was also supported by the different patient profiles at baseline (see Table 1).

Limitation and Strength of the Study

The main limitation of our study is the use of prebronchodilator spirometric values for defining COPD, instead of postbronchodilator values as suggested by the guidelines. As a consequence, subjects with asthma with fully reversible obstruction could have been falsely classified as COPD (34). We took the following precautions to avoid this potential bias: (I) All subjects who reported a diagnosis of asthma during their lifetime at baseline or at the end of the follow-up were excluded, and (2) a subject was classified as COPD only if his/her prebronchodilator FEV₁/FVC ratio was below the spirometric limit in both studies (9 years apart). Accordingly, even if we cannot rule out that some cases of undiagnosed asthma with transient airway obstruction at both surveys could have been present among our subjects with COPD, it is extremely unlikely that our results could be biased due to this.

Other limitations could be related to the small sample size for some subgroup analyses, to the duration of the follow-up (8.9 years on average), to the low number of subjects with moderate COPD, and to the relatively young age of our subjects. Accordingly, we are not sure that our conclusions can be applied to longer periods and to different age groups.

As in other longitudinal studies, the participation rate was low in some centers, and hence a potential selection bias could be present. However, this could have influenced our findings only to a minor extent because they were confirmed when the centers with the lowest participation rate were excluded.

The main strengths are the population-based prospective nature of our study and its highly standardized multicenter international framework.

Conclusion

In the international ECRHS cohort of young adults without asthma, those with the same spirometric diagnosis of mild/moderate COPD show a different lung function decline and different hospitalization rates. Our findings suggest that the two current spirometric definitions of COPD may include a non-negligible percentage of subjects with no clinically relevant disease (asymptomatic nonsmokers). Although respiratory symptoms were predictive of outcomes in subjects with COPD, smoking was the main factor influencing poor lung function and hospitalization.

Conflicts of Interest Statement: R.d.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.M.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.J. received $1,001–$5,000 from GlaxoSmithKline, $1,001–$5,000 from AstraZeneca, $1,001–$5,000 from MSD, $1,001–$5,000 from Boehringer Ingelheim, and $1,001–$5,000 from Pfizer in lecture fees and $10,001–$50,000 from GlaxoSmithKline in industry-sponsored grants. D.J. received $1,001–$5,000 in lecture fees from GlaxoSmithKline. N.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.L. received up to $1,000 from GlaxoSmithKline for a Specialist symposium, Denmark, February 2009. A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.B. received $1,001–$5,000 for providing technical advice from GlaxoSmithKline and up to $1,000 from AstraZeneca in lecture fees.

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