

## Cardiovascular Risk Factors in Chronic Obstructive Pulmonary Disease: Results of the ARCE Study

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**OBJECTIVE:** Cardiovascular disease is a common cause of death in patients with chronic obstructive pulmonary disease (COPD). It is not clear whether the high cardiovascular comorbidity is due to an increase in traditional risk factors or whether, in contrast, COPD can be considered an independent risk factor. The aim of this study was to analyze the prevalence of risk factors and cardiovascular comorbidity in a community-based population treated for COPD.

**PATIENTS AND METHODS:** This was a concurrent multicenter, cross-sectional study that included 572 patients with confirmed diagnosis of COPD. Information on cardiovascular risk factors and comorbidity was collected by extracting data from the medical records of the participating center.

**RESULTS:** The mean (SD) forced expiratory volume in 1 second (FEV<sub>1</sub>) was 53.7% (16.85%) of predicted and the ratio of FEV<sub>1</sub> to forced vital capacity was 57.9% (10.9%). Hypertension was reported in 53%, obesity in 27%, dyslipidemia in 26%, and diabetes in 23% of the patients. The prevalence of risk factors was not related to disease severity, but there was a trend towards an association with age. In the study group, 16.4% had ischemic heart disease, 7% cerebrovascular disease, and 17% peripheral vascular disease. Cardiovascular disease was not associated with COPD severity, but such an association was reported for age and traditional risk factors.

**CONCLUSIONS:** Cardiovascular risk factors are highly prevalent in patients with COPD. The prevalence of cardiovascular and cerebrovascular disease exceeds that

reported in the general population. No relationship was found between the severity of airflow obstruction and the presence of cardiovascular comorbidity.

**Key words:** COPD. Cardiovascular risk. Prevalence.

### Asociación de factores de riesgo cardiovascular y EPOC. Resultados de un estudio epidemiológico (estudio ARCE)

**OBJETIVO:** La enfermedad cardiovascular es una causa de muerte frecuente en los pacientes con enfermedad pulmonar obstructiva crónica (EPOC). No está claro si el exceso de comorbilidad cardiovascular se relaciona con un incremento de factores de riesgo clásicos o si, por el contrario, la EPOC puede considerarse un factor de riesgo independiente. El objetivo de este estudio ha sido analizar la prevalencia de factores de riesgo y comorbilidad cardiovascular en una población atendida en la comunidad por presentar EPOC.

**PACIENTES Y MÉTODOS:** Se ha realizado un estudio multicéntrico, concurrente y transversal, en el que se incluyó a 572 pacientes con diagnóstico confirmado de EPOC. Se recogieron datos de factores de riesgo y comorbilidad cardiovascular extraídos de la historia clínica del centro.

**RESULTADOS:** El valor medio  $\pm$  desviación estándar del volumen espiratorio forzado en el primer segundo era del 53,7  $\pm$  16,85% y la relación volumen espiratorio forzado en el primer segundo/capacidad vital forzada del 57,9  $\pm$  10,9%. La prevalencia de hipertensión arterial era del 53%, la de obesidad del 27%, la de dislipemia del 26% y la de diabetes del 23%. La prevalencia de factores de riesgo no se relacionó con la gravedad de la enfermedad, pero sí había una tendencia de asociación con la edad. La prevalencia de cardiopatía isquémica fue del 16,4%, la de enfermedad cerebrovascular del 7% y la de enfermedad vascular periférica del 17%. La prevalencia de comorbilidad vascular no se relacionó con la gravedad de la enfermedad, pero sí con la edad y los factores de riesgo clásicos.

**CONCLUSIONES:** Los pacientes con EPOC muestran una elevada prevalencia de factores de riesgo cardiovascular. La

This study was conducted under the auspices of the Society of Pulmonology and Thoracic Surgery of Madrid (NEUMOMADRID) and sponsored by Laboratorios Esteve. Pilar de Lucas Ramos and José Luis Izquierdo Alonso have contributed equally to performing this study.

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Manuscript received April 30, 2007. Accepted for publication October 31, 2007.

**prevalencia de enfermedad cardiovascular y cerebrovascular excede la comunicada en población general. No se ha observado relación entre la gravedad de la obstrucción al flujo aéreo y la presencia de comorbilidad cardiovascular.**

**Palabras clave:** EPOC. Riesgo cardiovascular. Prevalencia.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death in developed countries.<sup>1,2</sup> In recent years, it has been observed that many patients with COPD ultimately die from cardiovascular causes—from ischemic heart disease in particular.<sup>3,4</sup> A possible explanation for the association of COPD and cardiovascular disease can be found in exposure to cigarette smoke, a risk factor for both. However, reduced forced expiratory volume in 1 second (FEV<sub>1</sub>) is a well-known risk factor for the development of ischemic heart disease that is independent of smoking habit.<sup>5</sup> Inflammation was proposed as the link between the 2 processes when it was shown that high concentrations of inflammatory mediators in circulating blood were present in COPD patients. In addition, observational cohort studies based on health care databases have shown that the classic factors of cardiovascular risk—that is, obesity, diabetes, hypertension—are present more often in patients with COPD.<sup>6</sup> These same studies have reported that the increase in morbidity and mortality due to ischemic heart disease in patients with COPD is related to the presence of these risk factors. Therefore, the possible link between COPD and cardiovascular disease remains to be clarified.<sup>7</sup>

To date, no epidemiological studies of this type have been conducted in Spain and—as is the case for data on the incidence and prevalence of cardiovascular disease in the general population—the corresponding data for COPD might not be applicable to those reported for populations in North America. The aim of this study was to analyze the prevalence of cardiovascular risk factors and concurrent disease in a population diagnosed with COPD with a view to determining whether the severity of airflow obstruction might be related to the presence of this group of diseases.

## Patients and Methods

### Study Design and Population

The Cardiovascular Risk Factors in COPD Study (abbreviated to ARCE in Spanish) was a concurrent multicenter, cross-sectional study performed at 2 levels of health care—primary and specialized (pulmonology)—in the Community of Madrid and Guadalajara, Spain, with the participation of 60 primary health care physicians and 40 specialist physicians.

We included patients with prior diagnosis of COPD who met the following inclusion criteria: age over 40 years, active smoker or ex-smoker of more than 10 pack-years, ratio of FEV<sub>1</sub> to forced vital capacity (FVC) of less than 70% after bronchodilator challenge, prior follow-up by the treating physician for more than 1 year, and ability to understand the study and perform the study procedures. Patients with chronic respiratory disease other than COPD, including sleep apnea-hypopnea syndrome and history of atopy (rhinitis, asthma), were excluded.

To avoid selection bias, the physicians participating in the study included the patients consecutively according to the order in which they were seen in the clinic, until reaching the prespecified upper limit of 10 patients per physician, without any selection criteria other than the ones described above as inclusion or exclusion criteria. In order to avoid seasonal influence, recruitment was completed in the space of 1 month.

The study was approved by the hospital research ethics committee of the coordinating center, the Hospital Gregorio Marañón, Madrid, Spain, and all patients signed an informed consent prior to study participation.

### Procedures

A detailed medical history was taken of all patients using a specifically designed questionnaire, which included the following data: age, sex, smoking habit, weight, height, associated cardiovascular risk factors (hypertension, diabetes, dyslipidemia), presence of concurrent cardiovascular and cerebrovascular disease, dyspnea evaluated with the modified Medical Research Council scale, exacerbations and health resource usage in the past year, and medication related to COPD and cardiovascular disease. Similarly, the lung function test results were recorded and the patients were stratified according to 4 degrees of severity based on to the Global Obstructive Lung Disease guidelines.

The protocol stipulated that all patients should have been followed for at least 1 year, and so all study data, except the dyspnea questionnaire, could be obtained from the medical records of the participating centers, although data were confirmed on inclusion. The diagnosis of COPD had to be confirmed by lung function tests for classification of the patients according to stages, but no explicit criteria other than those used by each participating physician were established for diagnosis of risk factors and/or concurrent diseases.

### Statistical Analysis

A descriptive analysis was undertaken of all study variables using the usual statistics. Qualitative variables were expressed as absolute frequencies and percentages, whereas quantitative ones were expressed as means (SD) or as medians and percentiles. The Kolmogorov-Smirnov test was used to determine whether numeric variables were normally distributed. The means of 2 groups were compared using the *t* test for independent measures. The means of 3 or more groups were compared by analysis of variance with the Bonferroni correction. For comparison of proportions, the  $\chi^2$  test for linear trends or the Fisher exact test was used according to the sample size of the groups. The association between quantitative variables was studied with the Pearson or Spearman correlation coefficient according to whether or not the data were normally distributed. In all cases, differences were considered significant when the *P* value resulting from the test was less than or equal to .05.

## Results

In total, 851 patients were included in the study but the FEV<sub>1</sub>/FVC ratio, a variable needed for diagnosis of COPD, had been recorded for only 674. Of these, only 572 had a value of FEV<sub>1</sub>/FVC less than 70% and so met the criterion for inclusion in the analysis.

Of the 572 patients analyzed, 478 (85%) were men and 84 (15%) were women; 92% reported being a smoker or ex-smoker, whereas 6.8% were non-smokers. Most patients were at a moderate or severe stage of the disease, with a mean (SD) FEV<sub>1</sub> of 53.7% (16.8%) and FEV<sub>1</sub>/FVC of

TABLE 1  
Anthropometric Characteristics and Lung Function Data for the Study Population (n=572)<sup>a</sup>

Characteristic	
Mean age, y	68.3 (10.9)
Age group, y	
<40	2 (0.4%)
40-49	27 (4.8%)
50-59	105 (18.5%)
60-69	141 (24.8%)
>70	293 (51.6%)
Sex	
Male	478 (84.9%)
Female	85 (15.1%)
Weight, kg	75.7 (14)
Height, cm	165.3 (7.7)
BMI, kg/m <sup>2</sup>	27.7 (4.8)
Smoking habit	
Current	127 (22.2%)
Ex-smoker	399 (69.8%)
Never	39 (6.8%)
DK/NR	7 (1.2%)
Lung function	
FEV <sub>1</sub> (%)	53.7 (16.8)
FVC, %	70.3 (18.5)
FEV <sub>1</sub> /FVC, %	57.9 (10.9)
GOLD stage	
I (FEV <sub>1</sub> % >80%)	15 (3.2%)
II (FEV <sub>1</sub> % 50%-80%)	271 (57.8%)
III (FEV <sub>1</sub> % 30%-50%)	142 (30.3%)
IV (FEV <sub>1</sub> % <30%)	41 (8.7%)

Abbreviations: BMI, body mass index; DK/NR, don't know/no response; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative on Obstructive Lung Disease.

<sup>a</sup>Data are shown as number of patients (%) or mean (SD).

57.9% (10.9%). The anthropometric and lung function data are shown in Table 1.

### Cardiovascular Risk Factors

Cardiovascular risk factors other than smoking that were present were hypertension (53.3%), dyslipidemia (35%), obesity (26.9%) defined as a body mass index (BMI) of 30 kg/m<sup>2</sup> or higher, and diabetes (22%). On stratification of the patients by disease severity, no significant differences were found between groups for any of the risk factors

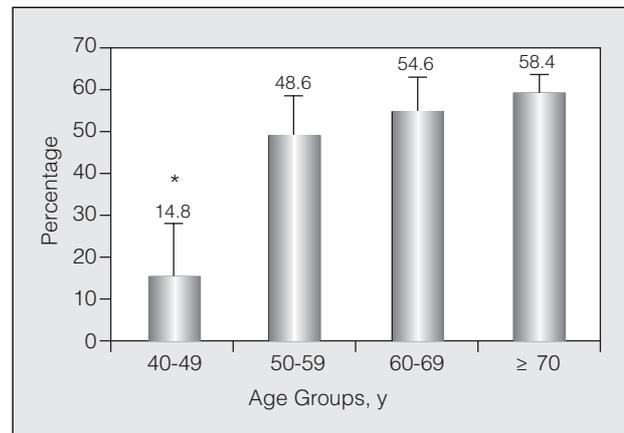


Figure 1. Frequency of arterial hypertension, stratified by age. \**P*<.05. Patients aged 40-49 years had a significantly higher frequency than patients in the other age groups

considered (Table 2). In contrast, there was an association with age, such that older age groups tended to show higher levels of cardiovascular risk in all factors (Table 3). This trend was statistically significant in the case of hypertension (Figure 1).

### Concurrent Cardiovascular Disease

The prevalences of concurrent cardiovascular and cerebrovascular disease were 17.7% for peripheral vascular disease, 16.4% for ischemic heart disease (within this category, 3% had suffered acute myocardial infarction), and 7% for cerebrovascular disease. As was the case for cardiovascular risk factors, there were no differences in prevalence between the different disease severity groups (Table 2). The prevalence of vascular disease increased with age (Table 3), however, as was also the case for risk factors. Furthermore, a significantly higher percentage of patients aged over 70 years had ischemic heart disease and cerebrovascular disease compared to patients aged less than 70 years (*P*<.05) (Figure 2).

TABLE 2  
Cardiovascular Risk Factors and Concurrent Disease, Stratified by Severity of Airflow Obstruction

Degree of Severity	I (FEV <sub>1</sub> >80%)	II (FEV <sub>1</sub> : 50%-80%)	III (FEV <sub>1</sub> : 30%-50%)	IV (FEV <sub>1</sub> <30%)
No. of patients	15	271	142	41
Hypertension	9 (60%)	143 (52.8%)	75 (52.8%)	13 (31.7%)
Dyslipidemia	8 (53.3%)	104 (38.4%)	47 (33.1%)	9 (22%)
Diabetes	4 (26.7%)	60 (22.1%)	27 (19%)	6 (14.6%)
Body mass index ≥30 kg/m <sup>2</sup>	3 (21.4%)	77 (29.1%)	29 (20.4%)	6 (14.6%)
Ischemic heart disease				
No	12 (80%)	215 (79.3%)	114 (80.3%)	36 (87.8%)
Yes	2 (13.3%)	49 (18.1%)	24 (16.9%)	5 (12.2%)
Don't know/no response	1 (6.7%)	7 (2.6%)	4 (2.8%)	0 (0%)
Arrhythmias	1 (6.7%)	39 (14.4%)	21 (14.8%)	5 (12.2%)
Heart failure	2 (13.3%)	44 (16.2%)	26 (18.3%)	9 (22%)
Acute cerebrovascular accident	0 (0%)	17 (6.3%)	12 (8.5%)	0 (0%)
Peripheral vascular disease	3 (20%)	48 (17.7%)	18 (12.7%)	4 (9.8%)

Abbreviation: FEV<sub>1</sub>, forced expiratory volume in 1 second.

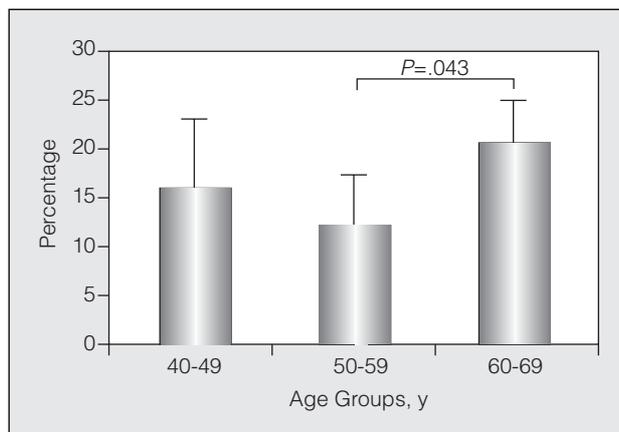


Figure 2. Frequency of ischemic heart disease, stratified by age. Patients aged 70 years or more had a higher rate; this difference was statistically significant with respect to the 60-69 year-old age group.

According to a univariate logistic regression analysis, age, BMI of 30 kg/m<sup>2</sup> or higher, hypertension, diabetes, and dyslipidemia were risk factors for ischemic heart disease; FEV<sub>1</sub> deterioration and smoking intensity reflected in pack-years were not predictors, however. In the

multivariate analysis, only age and dyslipidemia remained as independent risk factors ( $P < .05$ ) (Table 4).

With regard to cerebrovascular disease, age and presence of dyslipidemia were risk factors in the univariate analysis, but only age remained as a risk factor in the multivariate analysis ( $P < .05$ ).

### Discussion

This study showed that patients with COPD had a higher prevalence of cardiovascular risk factors than are found in similar age groups of the general population. We observed a high prevalence of cardiovascular disease in these patients, whereas the prevalence of cerebrovascular disease was similar to that of the general population. Age and the classic cardiovascular risk factors were associated with increased cardiovascular disease but not with the severity of airflow limitation.

COPD is a social and public health problem of top priority. In Spain, it is the fifth leading cause of death among men, with an annual mortality rate of 60 per 100 000 population, and the seventh leading cause among women, with an annual mortality rate of 17 per 100 000 population.<sup>1,2</sup> Exacerbations of COPD and/or respiratory

TABLE 3  
Cardiovascular Risk Factors and Concurrent Disease, Stratified by Age Group

Age, y	40-49	50-59	60-69	≥70
No. of patients	27	105	141	293
Hypertension	4 (14.8%) <sup>a</sup>	51 (48.6%) <sup>a</sup>	77 (54.6%) <sup>a</sup>	171 (58.4%) <sup>a</sup>
Dyslipidemia	6 (22.2%)	40 (38.1%)	57 (40.4%)	96 (32.8%)
Diabetes	4 (14.8%)	23 (21.9%)	30 (21.3%)	66 (22.5%)
Body mass index ≥30 kg/m <sup>2</sup>	5 (20%)	35 (34.3%)	32 (23.2%)	75 (26.5%)
Ischemic heart disease				
No	27 (100%)	87 (82.9%)	123 (87.2%)	224 (76.5%) <sup>c</sup>
Yes	0 (0%)	17 (16.2%)	17 (12.1%)	60 (23.3%)
Don't know/no response	0 (0%)	1 (1%)	1 (0.7%)	9 (3.1%)
Arrhythmias	1 (3.7%)	9 (8.6%)	14 (9.9%)	58 (19.8%)
Heart failure	0 (0%)	10 (9.5%)	20 (14.2%)	70 (23.9%) <sup>b</sup>
Acute cerebrovascular accident	1 (3.7%)	3 (2.9%)	3 (2.1%)	32 (10.9%) <sup>c</sup>
Peripheral vascular disease	1 (3.7%)	16 (15.2%)	23 (16.3%)	58 (19.8%)

<sup>a</sup>Statistically significant differences ( $P < .05$ ) with 40-49 year-old age group.

<sup>b</sup>Statistically significant differences ( $P < .05$ ) with 50-59 year-old age group.

<sup>c</sup>Statistically significant differences ( $P < .05$ ) with 60-69 year-old age group.

TABLE 4  
Risk Factors for Ischemic Heart Disease: Univariate and Multivariate Analysis

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Age	1.03	1-1.05	.017	1.04	1-1.07	.025
Sex (male)	1.35	0.69-2.66	.383	2.53	0.71-9.05	.154
Severity			.796			.716
I (FEV <sub>1</sub> >80%)	1	—	—	1	—	—
II (FEV <sub>1</sub> 50%-80%)	1.43	0.31-6.56	.642	3.29	0.38-28.18	.277
III (FEV <sub>1</sub> 30%-50%)	1.32	0.28-6.24	.724	2.84	0.32-25.09	.349
IV (FEV <sub>1</sub> <30%)	0.9	0.16-5.24	.909	2.65	0.25-28.56	.422
Body mass index	1.94	1.21-3.1	.006	1.53	0.8-2.94	.199
Hypertension	2.6	1.6-4.24	.000	1.86	0.96-3.59	.064
Dyslipidemia	3.26	2.05-5.18	.000	2.67	1.44-4.96	.002
Diabetes	2.32	1.43-3.77	.001	1.08	0.54-2.13	.831
Smoking, pack-years	1	1-1	.701	1	1-1	.963

Abbreviations: CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; OR, odds ratio.

failure had been assumed to be the ultimate cause of death in patients with COPD, in view of data obtained in patients who were admitted to hospital for respiratory failure.<sup>8</sup> More recent studies have shown that cardiovascular diseases, along with lung cancer, are among the main causes of death in COPD patients not selected by severity criteria.<sup>3,4,9,10</sup> These findings have been recently confirmed by the TORCH (Towards a Revolution in COPD Health) controlled trial, in which cardiovascular disease was the second leading cause of death among patients with moderate or severe disease.<sup>11</sup>

It has been postulated that the oxidative stress and systemic inflammation accompanying COPD could be the link with cardiovascular diseases—thus the 2 processes would share the same pathogenesis. It has been observed that patients with COPD, unlike smokers with no airflow obstruction, have concentrations of C-reactive protein above 3 mg/L, which is considered a high risk finding for the development of cardiovascular diseases.<sup>12-15</sup> In line with these findings, several observational studies have found that FEV<sub>1</sub> can be a predictor of coronary artery disease, and that this variable may be an even better predictor than already established risk factors such as serum cholesterol.<sup>16-18</sup>

On the other hand, other factors whose importance cannot be accurately determined may explain the negative effect of COPD on the cardiovascular system. In effect, smoking, which is reported by almost all patients, besides being independently associated with cardiovascular disease, is also associated with higher blood pressure. In contrast, lack of physical exercise, a common finding in patients with COPD, may in itself be a factor associated with higher mortality in these patients.<sup>19</sup> Other situations associated with cardiovascular risk also seem to be present in patients with COPD. In a case-control study performed in the United Kingdom, the 2699 patients with COPD (46% of whom were active smokers) had a higher incidence of comorbidity.<sup>20</sup> In another case-control series, patients with COPD had smoked more cigarettes and had a higher prevalence of coronary artery disease, heart failure, neoplastic disease, neurological diseases, and gastrointestinal diseases (3.7 chronic processes in the COPD group compared to 1.8 in the control group).<sup>21</sup> Antonelli-Incalzi et al<sup>22</sup> investigated patients discharged from hospital after a COPD exacerbation and found that the main concurrent diseases in patients were hypertension (28%), diabetes mellitus (14%), and ischemic heart disease (10%). Finally, Curkendall et al<sup>23</sup> conducted a retrospective study in Canada with a cohort of patients diagnosed with COPD and found that disease severity, defined according to clinical criteria, was associated with myocardial infarction and cardiovascular death even after adjustment for cardiovascular risk.<sup>23</sup>

Our study showed that patients with COPD had a higher prevalence of cardiovascular risk factors than that reported in the general population. The prevalence of hypertension in our study—53%—is higher than that reported not only after survey studies but also after studies in which the data has been confirmed by physical examination. Thus, the prevalence of hypertension was reported as 44% in a recent Spanish study (abbreviated in Spanish to VERIFICA) of the validity of an adaptation of the Framingham

cardiovascular risk equation.<sup>24</sup> The prevalence corresponded to confirmed data on cardiovascular risk factors collected from a group of 5732 subjects representative of the Spanish population, including subjects living in the Community of Madrid where the present study was conducted. Likewise, the prevalence of diabetes and obesity in the patients of our study exceeded that reported for the general adult population. In the case of diabetes, we found an overall prevalence of 23%, whereas in studies based on blood-glucose measurement, overall prevalences of 10% have been reported.<sup>25</sup> Although comparisons of different age groups are difficult with the information available, the differences appeared particularly in the population group aged between 50 and 69 years. The prevalence of obesity in our study was 27%, which is much higher than the figure of 14.5% published by the Spanish Society for the Study of Obesity<sup>26</sup> using the same definition as ours (BMI  $\geq 30$  kg/m<sup>2</sup>).

The interpretation of our results is limited by the greater exposure to smoking in our group compared to the general population. In addition, when we compare our findings with those of the aforementioned studies there are also differences in methodology that limit interpretability, given that our results are based on taking a medical history and, even in view of the current standardization of diagnostic criteria, except for BMI, we cannot rule out the application of different criteria. Other studies that show an even lower prevalence of risk factors in the general population are based on survey data, which gives rise to great variability and makes comparison with our results even more difficult.

In the analysis of cardiovascular comorbidity, like other authors, we found higher incidences of ischemic heart disease than in the general population. Although no data are available on the prevalence of myocardial infarction, there is a study that reported a prevalence of ischemic heart disease of 7%.<sup>28,29</sup> which is clearly lower than in our study. In contrast, the prevalence of cerebrovascular disease in our study is in line with that described in population groups of similar demographic characteristics. As was the case with cardiovascular risk factors, the main limitation for comparing our results with others' lies in the fact that few data are available for the general population and the information that is available is generally based on surveys.

In contrast to the findings of other studies,<sup>23</sup> we did not observe any association between severity of airflow obstruction, as indicated by the extent of deterioration of FEV<sub>1</sub>, and the presence of cardiovascular complications. However, age, a BMI of 30 kg/m<sup>2</sup> or higher, hypertension, diabetes, and dyslipidemia were risk factors for ischemic heart disease. The significant loss of valid cases for analysis, explainable by the continuing limited use of spirometry in primary health care in Spain, may lead to loss of statistical power in the comparison between the extent of deterioration of lung function and the presence of cardiovascular disease, but with the data available, not even a trend is apparent.

In conclusion, our data confirm that patients with COPD have a high prevalence of cardiovascular risk factors and ischemic heart disease. Ischemic heart disease is associated with cardiovascular risk factors and age, but we did not find any association with severity of obstruction. The results are limited in that this was an uncontrolled

observational study and so should be considered as merely preliminary, useful for formulating hypotheses. Further studies would be needed using a case-control methodology or with a longitudinal design to determine whether there really is an independent association between COPD and cardiovascular disease.

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