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Original research article

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Please cite this article as: Cosío BG, Casanova C, Soler-Cataluña J, *et al*. Unravelling young COPD and pre-COPD in the general population. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00334-2022).

Unravelling young COPD and pre-COPD in the general population

Authors: Borja G. Cosío* (1,2), Ciro Casanova* (3), Juan José Soler-Cataluña (2,4), Joan B Soriano (2,5), Francisco García-Río (2,6), Pilar de Lucas (7), Inmaculada Alfageme (8), José Miguel Rodríguez González-Moro (9), Guadalupe Sánchez (10), Julio Ancochea (2,5), Marc Miravitlles (11,2)

Centres: 1. Servicio de Neumología, Hospital Universitario Son Espases-IdISBa, Palma de Mallorca; 2. CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III (ISCIII), Madrid; 3. Servicio de Neumología, Hospital Universitario Nuestra Señora de Candelaria, Tenerife; 4. Servicio de Neumología, Hospital Arnau de Vilanova-Lliria, Valencia; 5. Servicio de Neumología, Hospital Universitario La Princesa; Universidad Autónoma de Madrid, Madrid; 6. Servicio de Neumología, Hospital Universitario La Paz-IdiPAZ, Madrid; 7. Servicio de Neumología, Hospital General Gregorio Marañon, Madrid; 8. Unidad de Gestión Clínica de Neumología, Hospital Universitario Virgen de Valme, Universidad de Sevilla, Sevilla; 9. Servicio de Neumología, Hospital Universitario "Príncipe de Asturias". Alcalá de Henares. Universidad de Alcalá. Madrid; 10. Departamento Médico, GSK, Tres Cantos, Madrid; 11. Pneumology Department, Hospital Universitari Vall d´Hebron/Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona; all in Spain.

Correspondence: Borja G Cosío, Servicio de Neumología, Hospital Universitario Son Espases-IdISBa, Palma de Mallorca

* Co-primary authors

Abstract

Background. Chronic obstructive pulmonary disease (COPD) is commonly diagnosed when the airflow limitation is well established and symptomatic.

Aim. We aimed to identify individuals at risk of developing COPD according to the concept of pre-COPD and compare their clinical characteristics with *(1)* those who have developed the disease at a young age, and *(2)* the overall population with and without COPD.

Methods. The EPISCAN II study is a cross-sectional, population-based study aimed to investigate the prevalence of COPD in Spain in subjects≥ 40 years. Pre-COPD was defined as the presence of emphysema>5% and/or bronchial thickening by CT scan and/or DLCO<80% in subjects with respiratory symptoms and post-bronchodilator FEV_1/FVC>0.70. Young COPD, was defined as FEV_1/FVC<0.70 in a subject ≤50 years. Demographic and clinical characteristics were compared among pre-COPD, Young COPD and the overall population with and without COPD.

Results. Among the 1,077 individuals with FEV_1/FVC<0.70, 65 (6.0%) were ≤ 50 years. Among the 8,015 individuals with FEV_1/FVC>0.70, 350 underwent both DLCO test and chest CT scan. Of those, 78 (22.3%) subjects fulfilled the definition of pre-COPD. Subjects with pre-COPD were older, predominantly women, less frequently active or ex- smokers, with less frequent previous diagnosis of asthma but with higher symptomatic burden than those with Young COPD.

Conclusions. 22.3% of the studied population was at risk of developing COPD, with similar symptomatic and structural changes than those with well-stablished disease

without airflow obstruction. This COPD at risk population is different from those that develop COPD at young age.

Take home message

Subjects fulfilling the definition of pre-COPD show similar symptomatic and structural changes than those with well-stablished disease without any evidence of airway obstruction. The fixed ratio of FEV1/FVC definition for COPD is missing an important group of patients that have significant disease.

Introduction

COPD is a prevalent lung condition traditionally associated to cigarette smoke that usually remains underdiagnosed or is diagnosed in advanced stages of the disease process[1,2]. Noteworthy, most patients are diagnosed in the sixth or seventh decade of life when symptoms are bothersome, or exacerbations appear. We have recently described the prevalence of COPD in Spain, that affects 11.8% of adults 40 years and older randomly selected from the general population[3]. 78% of COPD had not been diagnosed before[3]. The mean age of the COPD population was 65 years old, an age when structural and functional changes in the lungs and other organs affected by the presence of COPD are mostly non-reversible.

For this reason, it has been claimed that we should look at COPD "upstream in the river" (Bartolome Celli *dixit*)[4] and a number of definitions of Early COPD have been proposed[5], aiming to, on the one hand, rise attention of the early origins of the disease and, on the other hand, to point out that we are arriving late to initiate a disease-modifying therapy for COPD[6], or a preventive measure such as smoking cessation.

However, the search for an early identification of those patients at risk of developing COPD remains controversial. Attempts to define a GOLD 0 stage, based on the symptomatic and healthcare burden of smokers with normal spirometry failed to demonstrate to be an effective strategy[7].Nevertheless, a number of cohort studies have found associations between respiratory symptoms [8] or low DLCO[9] and the development of COPD. More recently, the concept of pre-COPD, that includes not only

symptoms but also structural or functional abnormalities compatible with those found in COPD, has been proposed[10] as a risk marker of developing the disease.

A better knowledge of the natural history of the disease should clarify whether the development of COPD is a continuum that starts at young age with a patient with symptoms and no airflow limitation, of whom some of them will progress to parenchymal abnormalities and airflow obstruction.

We aimed to identify patients at risk of developing COPD according to the concept of pre-COPD in a large cohort of well characterized patients taken from the general population and compare their clinical characteristics with those who have developed the disease at a young age and with the overall population with or without COPD.

Methods

Population

The EPISCAN II study is a national, multicentre, cross-sectional, population-based epidemiological study aimed to investigate the prevalence and determinants of COPD in Spain. The protocol, fieldwork and methods have been described elsewhere[11]. Briefly, the fieldwork was conducted from April 2017 to February 2019 in 20 teaching hospitals throughout Spain. Subjects from the general population who were resident in the postal code areas nearest the participating hospitals were selected. The inclusion criteria were as follows: men or women aged 40 years or older with no physical or

cognitive difficulties that would prevent them from completing spirometry or any of the study procedures. A randomized sample of 400 COPD and 400 non-COPD participants in the short-visit from 12 preselected sites were invited to complete further testing in a long-visit, according to quotas of age (10-yr. strata) and sex. Tests included single-breath CO diffusing capacity (DLCO) and computed tomography (CT) scan of the thorax. The study was approved by the ethics committees of each of the participating centers, and all participants provided informed consent. The EPISCAN II protocol is registered at https://clinicaltrials.gov (NCT03028207) and at www.gsk-clinicalstudyregister.com/study/205932.

For the purposes of this pre-specified secondary objective of EPISCAN II we defined Early COPD as Young COPD, meaning a post-bronchodilator $FEV_1/FVC<0.70$ in a subject younger than 50 years. Pre-COPD was defined according to Han et al definition[10] as the presence of emphysema>5% and/or presence of bronchial thickening in the CT scan and/or DLCO<80% in subjects with respiratory symptoms and a post-bronchodilator $FEV_1/FVC>0.70$. Bronchial thickening was considered when the measurement of airway thickness at the bronchiole level was greater or equal to the highest quartile of the sample. Respiratory symptoms were considered as the presence of cough and/or phlegm production and/or dyspnea (defined as mMRC >0 for <80 years and >1 for those ≥80 years old) or a CAT score>10.

Variables and Procedures

Demographic information on sex, age, level of education, comorbidities, weight, height and smoking were collected. Forced spirometry pre and post-bronchodilation was

performed using a pneumotachograph (Vyntus Spiro, Carefusion, Germany), according to standardized procedures as previously described (5,9). Single-breath CO diffusing capacity of the lung for carbon monoxide (DLCO) (MasterScreen diffusion, Carefusion, Germany was measured according to the ATS/ERS recommendations[12], and adjusted by haemoglobin levels and atmospheric pressure. Global Lung Function Initiative (GLI) equations were used as reference values[13] . Six minutes walking test was performed following ATS recommendations[14] and BODE index[15] was calculated accordingly. Computed tomography (CT) images were acquired during maximal inspiration, without contrast and with low-dose radiation, 120kVp as acquisition voltage. The images obtained underwent semi-automatic post-processing for determination of the percentage of emphysema, areas of extension, airway thickness, other measurements, and lung parenchyma attenuation and airway wall thickness, as previously described. For the diagnosis of respiratory symptoms, the answers to the European Community for Coal and Steel Questionnaire (ECSC) were used[16]. The diagnosis of cough was considered when the participant answered yes to any of the cough-related questions of the questionnaire. Specific questions for dyspnea and chronic bronchitis were included. The degree of dyspnea was evaluated by the modified Medical Research Council (mMRC) dyspnea scale[17]. Health status was assessed by the COPD Assessment Test (CAT) questionnaire[18]. The comorbidities were quantified by the Charlson and the COTE index[19,20]. Exacerbations in the previous year requiring the use of antibiotics and/or corticosteroids and the need of emergency visits or hospital admissions were registered.

Statistical Analysis

Categorical variables were presented as numbers with percentages, and continuous variables as mean with standard deviation (SD) or median (interquartile range), according to their distribution. The characteristics of the subgroups defined (pre-COPD and young COPD) have been compared using Student's t-test, U-Mann-Whitney test or $\chi 2$ test. In the case of the comparison between COPD, non-COPD and the subgroups defined, ANOVA and $\chi 2$ were used. Data were analysed with the Statistical Analysis System (SAS) Enterprise Guide 7.15, considering a statistical significance (p) of 0.05 for all comparisons.

Results

The EPISCAN II population included 9,092 subjects who were able to perform a valid spirometry. Of those, 728 (8.0%) subjects underwent DLCO and 668 (7.3%) chest CT scan. As previously shown, 11,8% of the EPISCAN II population fulfilled criteria for COPD. Figure 1 (flowchart)

Prevalence of young COPD

Among the 1,077 individuals with a post-bronchodilator $FEV_1/FVC<0.70$, 65 had 50 years or less (6% of the COPD population). Individuals had a mean (SD) age of 45.8 (2.6) years and 65% of them were symptomatic, as previously defined by the presence of cough with phlegm production or dyspnea or CAT≥10.

Prevalence of pre-COPD

Among the 8,015 individuals with a post-bronchodilator FEV_1/FVC>0.70 in a valid spirometry, 350 (4.4%) of them underwent both DLCO test and chest CT scan. Of those, 148 (42.3%) were symptomatic, 51 (14.6%) had a DLCO<80%, 101 (28.9%) had >5% emphysema and 40 (11.4%) had bronchial diameter>1,13 mm (value of the highest quartile) on chest CT scan. Seventy-eight (22.3%) subjects fulfilled the pre-specified definition of pre-COPD (Figure 2).

Characteristics of pre-COPD vs Young COPD

When comparing individuals with pre-COPD with those with Young COPD there were distinctions between these two (table 1): pre-COPD individuals were older, with median (interquartile range, IQR) age of 65 years (54-72) vs 46 (43-48) years (p<0.0001) respectively, and less frequently active or ex- smokers (57.6% vs 80%, p=0.0002), but with higher symptomatic burden as per MMRC dyspnea scale≥1, 61.5% vs 35.4% (p=0.01) (Table 1 and figure 3) or CAT (11.3 vs 9.1, p=0.03).

A previous diagnosis of asthma was referred by the patient in 29.2% vs 6.4% and median blood eosinophil count was higher 233 vs 158 cels/microL in the young COPD group compared to pre-COPD respectively (table 2). However, only 5.1% of pre-COPD patients were receiving treatment with short-acting beta-agonist or inhaled corticosteroids, whereas 26.2% and 15.4% of Young COPD were receiving them, respectively. No statistically significant differences were found in the history of exacerbations in the previous year, that tended to be higher in the Young COPD group compared to pre-COPD group (7.7% vs 2.6%, p=0.15) (Figure 3).

Characteristics of pre-COPD compared to the overall COPD and non-COPD population

When comparing the patients fulfilling criteria of pre-COPD with the overall COPD population, and the non-COPD (and non-pre-COPD) population, pre-COPD patients were more frequently female than the COPD population, with younger age, less frequently smoker or ex-smokers but similar symptomatic burden measured by mMRC dyspnea (Table 1 and figure 3). Pre-COPD and COPD had similar burden of comorbidities with higher Charlson and COTE index than the control population. Also, both pre-COPD and COPD have impaired exercise capacity measured by the 6 minutes walking test, with similar emphysema and lower DLCO (table 2). Pre-COPD also showed a higher bronchiole thickness than the control group. However, the pre-COPD group was similar to the control population without COPD in spirometric parameters, blood eosinophil counts, history of asthma or use of respiratory medication.

Characteristics of Young COPD compared to the overall COPD and non-COPD populations

Patients with COPD younger than 50 years, compared to a population without criteria for COPD nor pre-COPD, were more frequently males, more active or former smokers with more symptomatic burden measured by mMRC dyspnea and CAT score, had more comorbidities measured by means of the Charlson and COTE indexes and suffered more exacerbations (table 1 and figure 3). More frequently reported a past medical history of asthma and showed higher blood eosinophil count than controls.

In comparison with the overall COPD population, Young COPD had similar airflow limitation and similar symptomatic and exacerbation burden despite having better

exercise capacity, and therefore lower BODE index. Young COPD were less frequently treated with anticholinergics than the overall COPD population.

Discussion

Three important messages should be taken from this research: first, we have shown, for the first time that 22.3% of a subsample of the general population would qualify for the definition of pre-COPD, and this has important implications in terms of symptoms and health status in this untreated population. Second, we have also shown that 6% of the population that fulfills the criteria for a diagnosis of COPD are younger than 50 years, but this Young COPD population have similar symptomatic, exacerbation and comorbidity burden than the overall older COPD population. And third, that the pre-COPD population appears different from those that develop COPD at a young age.

Interpretation of novel findings

In this population-based study we have identified, within a randomized subgroup who underwent CT scan and DLCO, that 22.3% of this population have symptoms, reduced exercise capacity, emphysema and small airways thickness similar to the population with COPD despite not fulfilling spirometric criteria for COPD. This population is likely to be at high risk of developing COPD and its consequences, but we are not detecting them in a timely manner, which is reflecting a limitation of spirometry as a screener tool. Interestingly enough, we have also shown that 6% of the population with COPD are younger than 50 years, and they have a well-stablished disease with similar health-related outcomes than the older COPD population. Noteworthy, it is not possible to assume that the pre-COPD condition evolves to Young COPD, since pre-COPD are older, predominantly women with less smoking burden despite similar symptomatic and DLCO or structural impairment than the Young COPD population.

Previous studies

Martinez et al proposed to name Early COPD to those patients younger than 50 years with chronic airflow limitation and evidence of structural or progressive functional impairment such as visual emphysema, air trapping, bronchial thickening [21]. Soriano et al included the concept of disease activity as part of the concept of early COPD in an attempt to include exacerbations as part of the patient at risk profile[5]. However, as GOLD update 2022 underlines, early means "near the beginning of a process" and because COPD may start early in life, and takes a long time to be clinically manifested, determining if someone really suffers "early" COPD is challenging; therefore, it is more appropriate to label them as Young COPD[1].

A recent prospective, multicentre, case-control study [22,23]aimed to describe the characteristics of young COPD (defined only by age<50 years) that included smokers>10 packs-year with or without post-bronchodilator FEV1/FVC<0.70, found that these young COPD patients already had moderate airflow limitation and were often symptomatic, used healthcare resources frequently, had air trapping, reduced diffusing capacity and had frequent evidence of emphysema by computed tomography (CT) (61%). Of note, less than half of cases (46%) had been previously diagnosed with COPD. These observations were reproduced in the ECLIPSE and COPDGene cohorts[22].

Colak et al also found that, among individuals under 50 years of age and 10 pack-years or greater of tobacco consumption from the general population, 15% fulfill criteria of early COPD. Individuals with early COPD more often have chronic respiratory symptoms and severe lung function impairment, and an increased risk of acute respiratory hospitalizations and early death[24]. Depending on amount of smoking

exposure, 24% of young adults in the general population with early COPD develop clinical COPD 10 years later[25].

Previous attempts to identify individuals at risk of developing COPD have rendered different results. The COPDgene study found that 43% of smokers with normal FEV_1/FVC ratio had airwall thickening or emphysema on CT and 23% had mMMRC dyspnea score ≥2, and these patients had reduced exercise capacity and increased exacerbation-like events[26]. Also, in SPIROMICS near 50% of smokers with normal spirometry had similar symptomatic burden than those with COPD with mild or moderate airflow limitation [27]. A proportion of these symptomatic smokers also showed airway wall thickening on CT similar to our results.

The importance of symptoms without obstruction led to the concept of GOLD 0 or COPD at risk, and many studies have shown that a proportion ranging from 11.6 to 20.5% of these individuals develop COPD during follow-up[28,29]. This at risk status of GOLD 0 was initially considered but later abandoned, because the proportion of individuals that progressed to COPD was considered low and not different from those who were not considered as GOLD 0[10]. Noteworthy, we have been more precise than the proposal of pre-COPD on defining symptoms threshold using CAT and mMRC scores adjusted by age, since we have previously shown that this may imply an impact on mortality[17].

Other markers of risk for developing COPD have been previously explored, like physiologic measurements or imaging. A reduced single-breath DLCO test (<80% reference) in active smokers with normal spirometry followed over 45 months was found to be associated to a higher incidence of GOLD-defined COPD compared to

those with normal DLCO (22% vs 3%, respectively)[9]. Our population with pre-COPD have reduced DLCO in a similar extent that the whole COPD population, which supports the hypothesis that these individuals are more prone to develop GOLD-defined COPD.

Imaging is another way to identify patients at risk for developing GOLD-defined COPD. In different trials using CT scan for screening of lung cancer, smokers with no evidence of airflow limitation at baseline who developed COPD during follow-up had more emphysema on CT[3031]. Also, increased airway thickness measured by CT in those trials was significantly (and independently from the presence of emphysema) associated with incident COPD[32]. In keeping with these previous findings, our data support the importance of imaging in the new category of pre-COPD, showing a similar extent of emphysema and increased airway thickness than the COPD population. We used a 5% of quantified emphysema as a threshold to determine risk, as previously shown by Lynch et al [33].

We have included in our analysis the population with COPD younger than 50 years, assuming that lung growth and development reach its peak at around 20-25 years of age in men but at 15 years in women, and begin to decline later [34]. In population-based studies these younger individuals with COPD have more frequently a previous diagnosis of asthma, as we have found in our population. A “diagnosis of asthma” (not necessarily the disease) is frequently associated with abnormal lung development [35] and the latter is now a well-recognized cause of COPD [36].

Clinical implications

To identify subjects at risk of developing COPD and those with already established disease at early stages who are at risk of progressing may have important clinical implications. Very few therapeutic trials have been conducted in symptomatic individuals without airflow limitation. A recent published perspective by experts in the field highlights the need of RCTs focused on young COPD or Pre-COPD patients to reduce disease progression, providing innovative approaches to identifying and engaging potential study subjects[6]. Moreover, it has been recently suggested that this group of patients with symptoms and emphysema should be considered COPD despite not having evidence of airflow obstruction[37,38].

According to our results, different strategies should be implemented to identify this population at risk, since they show clear differences. Pre-COPD population are highly symptomatic individuals predominantly women with less smoking exposure whereas young COPD are patients with well-established disease at younger age with higher smoking burden and more frequently diagnosis of asthma.

Strengths and limitations

There are several strengths in this research, including novelty, an unbiased population approach, and the use of low dose CT scan and DLCO to characterize COPD beyond spirometry. It should be mentioned that similarities and differences of emphysema, DLCO, and bronchial thickness found in the Pre-COPD group were attributes used to define it. Moreover, a number of limitations should be considered. The main limitation of this study is the lack of longitudinal follow-up that could confirm that those fulfilling the criteria for Pre-COPD are really at higher risk of developing COPD. Nevertheless, the data showed here underlies the importance and impact of the disease in young

subjects taken from the general population and of those with respiratory symptoms and associated functional and/or structural abnormalities. Secondly, it is possible that the small sample size could limit the magnitude of the differences in some sub-analysis found between those with pre-COPD and young COPD due to potential type 1 and type 2 errors. Further, given the population approach, representativity of hospital-based and the most severe COPD patients is limited. Finally, it is possible that we may have underestimated the amount of emphysema by using LDCT[39]. Nevertheless, we think that this does not have a major impact in our findings.

Conclusions

We found that 22.3% of the studied population is at risk of developing COPD, with similar symptomatic and structural changes than those with well-stablished disease without any evidence of airway obstruction. This population at risk is different from those that develop COPD at young age. Different strategies to tackle with these two early faces of COPD should be considered. Also, our findings reflect that fixed ratio of FEV1/FVC definition for COPD is missing an important group of patients that have significant disease.

Acknowledgements

The EPISCAN II study was sponsored by GlaxoSmithKline. The collaboration of Monica Sarmiento and Neus Canal from IQVIA, and Carolina Peña and José Julio Jiménez from GSK is explicitly acknowledged.

The following investigators have participated in EPISCAN II:

Scientific Committee: Borja G. Cosio, Ciro Casanova, Inmaculada Alfageme, Pilar de Lucas, Julio Ancochea, Marc Miravitlles, Juan José Soler-Cataluña, Francisco García-Río, José Miguel Rodríguez González-Moro, Guadalupe Sánchez, and Joan B Soriano.

Bibliography

1. Halpin DMG, Criner GJ, Papi A, et al. Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2021;203(1):24-36. doi:10.1164/RCCM.202009-3533SO
2. Miravitlles M, Calle M, Molina J, et al. Spanish COPD Guidelines (GesEPOC) 2021: Updated Pharmacological treatment of stable COPD. *Arch Bronconeumol*. 2021;58(1):69-81. doi:10.1016/J.ARBRES.2021.03.005
3. Soriano JB, Alfageme I, Miravitlles M, et al. Prevalence and Determinants of COPD in Spain: EPISCAN II. *Arch Bronconeumol*. (Engl Ed). 2021 Jan;57(1):61-69. doi:10.1016/J.ARBRES.2020.07.024
4. Lange P, Celli B, Agustí A, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2015;373(2):111-122. doi:10.1056/nejmoa1411532
5. Soriano JB, Polverino F, Cosio BG. What is early {COPD} and why is it important? *Eur Respir J*. 2018;52(6):1801448. doi:10.1183/13993003.01448-2018
6. Martinez FJ, Agusti A, Celli BR, et al. Treatment Trials in Young Patients with COPD and Pre-COPD Patients: Time to Move Forward. *Am J Respir Crit Care Med*. October 2021. doi:10.1164/rccm.202107-1663SO
7. Pompe E, Strand M, van Rikxoort EM, et al. Five-year progression of emphysema and air trapping at ct in smokers with and those without chronic obstructive pulmonary disease: Results from the COPDGene study. *Radiology*. 2020;295(1):218-226. doi:10.1148/radiol.2020191429

8. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The Presence of Chronic Mucus Hypersecretion across Adult Life in Relation to Chronic Obstructive Pulmonary Disease Development. *Am J Respir Crit Care Med*. 2016;193(6):662-672. doi:10.1164/RCCM.201511-2210OC

9. Harvey BG, Strulovici-Barel Y, Kaner RJ, et al. Progression to COPD in smokers with normal spirometry/low DLCO using different methods to determine normal levels. *Eur Respir J*. 2016;47(6):1888-1889. doi:10.1183/13993003.00435-2016

10. Han MLK, Agusti A, Celli BR, et al. From GOLD 0 to pre-COPD. *Am J Respir Crit Care Med*. 2021;203(4):414-423. doi:10.1164/rccm.202008-3328PP

11. Alfageme I, de Lucas P, Ancochea J, et al. 10 Years After EPISCAN: A New Study on the Prevalence of COPD in Spain —A Summary of the EPISCAN II Protocol. *Arch Bronconeumol* (Engl Ed). 2019 Jan;55(1):38-47. doi:10.1016/j.arbres.2018.05.011

12. MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26(4):720-735. doi:10.1183/09031936.05.00034905

13. Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J*. 2017;50(3). doi:10.1183/13993003.00010-2017

14. Crapo RO, Casaburi R, Coates AL, et al. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117. doi:10.1164/AJRCCM.166.1.AT1102

15. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction,

dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(10):1005-1012. doi:10.1056/NEJMOA021322

16. Cotes JE, Chinn DJ. Questionnaire of the ECSC on respiratory symptoms. *Eur Respir J*. 1989;2(10):1021-1022.

17. Casanova C, Marin JM, Martinez-Gonzalez C, et al. Differential effect of modified Medical Research Council Dyspnea, COPD Assessment Test, and Clinical COPD Questionnaire for symptoms evaluation within the new GOLD staging and mortality in COPD. *Chest*. 2015;148(1). doi:10.1378/chest.14-2449

18. De Torres JP, Marin JM, Martinez-Gonzalez C, et al. Clinical application of the COPD assessment test: Longitudinal data from the COPD history assessment in Spain (CHAIN) Cohort. *Chest*. 2014;146(1). doi:10.1378/chest.13-2246

19. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47(11):1245-1251. doi:10.1016/0895-4356(94)90129-5

20. De Torres JP, Casanova C, Marín JM, et al. Prognostic evaluation of COPD patients: GOLD 2011 versus BODE and the COPD comorbidity index COTE. *Thorax*. 2014;69(9):799-804. doi:10.1136/THORAXJNL-2014-205770

21. Martinez FJ, Han MK, Allinson JP, et al. At the root: Defining and halting progression of early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;197(12):1540-1551. doi:10.1164/rccm.201710-2028PP

22. Cosío BG, Pascual-Guardia S, Borras-Santos A, et al. Phenotypic characterisation of early COPD: a prospective case–control study. *ERJ Open Res*. 2020;6(4):00047-02020. doi:10.1183/23120541.00047-2020

23. Borràs-Santos A, Garcia-Aymerich J, Soler-Cataluña JJ, et al. Determinants of the

Appearance and Progression of Early-Onset Chronic Obstructive Pulmonary Disease in Young Adults. A Case-Control Study with Follow-up. *Arch Bronconeumol*. (Engl Ed). 2019 Jun;55(6):312-318.

24. Çolak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prevalence, characteristics, and prognosis of early chronic obstructive pulmonary disease the Copenhagen general population study. *Am J Respir Crit Care Med*. 2020;201(6):671-680. doi:10.1164/rccm.201908-1644OC

25. Colak Y, Afzal S, Nordestgaard BG, Lange P, Vestbo J. Importance of Early COPD in Young Adults for Development of Clinical COPD Findings from the Copenhagen General Population Study. *Am J Respir Crit Care Med*. 2021;203(10):1245-1256. doi:10.1164/rccm.202003-0532OC

26. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med*. 2015;175(9):1539-1549. doi:10.1001/jamainternmed.2015.2735

27. Woodruff PG, Barr RG, Bleecker E, et al. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *N Engl J Med*. 2016;374(19):1811-1821. doi:10.1056/NEJMOA1505971

28. Vestbo J, Prescott E, Lange P, et al. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. *Am J Respir Crit Care Med*. 1996;153(5):1530-1535. doi:10.1164/AJRCCM.153.5.8630597

29. Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med*. 2002;166(3):329-332. doi:10.1164/RCCM.2112048

30. Mohamed Hoesein FAA, Van Rikxoort E, Van Ginneken B, et al. Computed tomography-quantified emphysema distribution is associated with lung function decline. *Eur Respir J*. 2012;40(4):844-850. doi:10.1183/09031936.00186311

31. McAllister DA, Ahmed FS, Austin JHM, et al. Emphysema predicts hospitalisation and incident airflow obstruction among older smokers: a prospective cohort study. *PLoS One*. 2014;9(4). doi:10.1371/JOURNAL.PONE.0093221

32. Mohamed Hoesein FAA, De Jong PA, Lammers JWJ, et al. Airway wall thickness associated with forced expiratory volume in 1 second decline and development of airflow limitation. *Eur Respir J*. 2015;45(3):644-651. doi:10.1183/09031936.00020714

33. Lynch DA, Austin JHM, Hogg JC, et al. CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society. *Radiology*. 2015;277(1):192-205. doi:10.1148/RADIOL.2015141579

34. Kohansal R, Martinez-Camblor P, Agustí A, Sonia Buist A, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med*. 2009;180(1):3-10. doi:10.1164/RCCM.200901-0047OC

35. Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med*. 2019;7(4):358-364. doi:10.1016/S2213-2600(18)30529-0

36. Martinez FD. Early-Life Origins of Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2016;375(9):871-878. doi:10.1056/NEJMRA1603287

37. Barnes PJ, Vestbo J, Calverley PM. The Pressing Need to Redefine “COPD”. *Chronic Obstr Pulm Dis (Miami, Fla)*. 2019;6(5):380-383. doi:10.15326/jcopdf.6.5.2019.0173

38. Lowe KE, Regan EA, Anzueto A, et al. COPDGene® 2019: Redefining the diagnosis of chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis*. 2019;6(5):384-399. doi:10.15326/jcopdf.6.5.2019.0149

39. Wisselink HJ, Pelgrim GJ, Rook M, et al. Ultra-low-dose CT combined with noise reduction techniques for quantification of emphysema in COPD patients: An intra-individual comparison study with standard-dose CT. *Eur J Radiol*. 2021;138. doi:10.1016/j.ejrad.2021.109646

Authors' contributions

The study concept and design: BGC, CC, MM, JJS-C, JBS, FG-R, PL, IA, JMG-M, GS, JA. Data acquisition: JJS-C, JA, BGC. Analysis and interpretation of the data: MM, JJS-C, JBS, BGC. Drafting of the manuscript: BGC and CC. Critical revision and approval for submission: MM, JJS-C, JBS, FG-R, PL, IA, CC, JMG-M, GS, JA, BGC. All authors have read and approved the final manuscript.

Funding

The EPISCAN II study was sponsored by GlaxoSmithKline (GSK).

Availability of data and materials

Information on the GSK data sharing commitments and requesting access to anonymized individual participant data and associated documents can be found at www.clinicalstudydatarequest.com.

DECLARATIONS

Ethics approval and consent to participate

The study was approved by the ethics committees of each of the participating centres, and all participants provided informed consent.

Consent for publication

Not applicable

Competing interests

Borja G Cosio has received speaker or consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Novartis, Sanofi, TEVA, and research grants from Menarini, AstraZeneca and Boehringer-Ingelheim. Ciro Casanova has received speaker or consulting fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Novartis, and research grants from GlaxoSmithKline, Menarini and AstraZeneca. Juan José Soler-Cataluña has received speaker fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Esteve, Ferrer, GlaxoSmithKline, Menarini, Novartis and Teva, and and consulting fees from AstraZeneca, Bial, Boehringer Ingelheim, GlaxoSmithKline, Ferrer and Novartis. Francisco García-Río has received speaker or consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Novartis, Pfizer and Rovi, and research grants from Chiesi, Esteve, Gebro Pharma, GlaxoSmithKline, Menarini and TEVA. Julio Ancochea has received speaker or consulting fees from Actelion, Air Liquide, Almirall, AstraZeneca, Boehringer Ingelheim, Carburos Médica, Chiesi, Faes Farma, Ferrer, GlaxoSmithKline, InterMune, Linde Healthcare, Menarini, MSD, Mundipharma, Novartis, Pfizer, Roche, Rovi, Sandoz, Takeda y Teva. Inmaculada

Alfageme has no conflicto of interest. Guadalupe Sanchez is a GSK employee within the Medical Department. Marc Miravitlles has received speaker or consulting fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Laboratorios Esteve, Gebro Pharma, Kamada, GlaxoSmithKline, Grifols, Menarini, Mereo Biopharma, Novartis, pH Pharma, Palobiofarma SL, Rovi, TEVA, Spin Therapeutics, Verona Pharma and Zambon, and research grants from Grifols.

Tables and figures

Table 1: Differential demographic and clinical characteristics of Young and Pre-COPD subjects compared to COPD and non-COPD populations.

	COPD (C) (n=1012)	Young COPD (YC) (n=65)	Pre-COPD (PC) (n=78)	Non-COPD (NC) (n=263)	P value				
					C versus YC	NC versus YC	C versus PC	NC versus PC	PC versus YC
General characteristics									
Age in years, mean (SD) 68.0 (59.0 ; 75.0)	67.8 (9.9)	45.8 (2.6) 46.0 (43.0 ; 48.0)	63.5 (11.6) 65.0 (54.0 ; 72.0)	59.3 (10.1) 59.0 (51.0 ; 67.0)	<0.0001	<0.0001	0.003	0.0002	<0.0001
Sex, female, %	418 (41.3%)	30 (46.2%)	44 (56.4%)	163 (62.0%)	0.44	0.02	0.009	0.37	0.22
BMI, mean (SD)	27.4 (4.6)	27.4 (7.0)	28.0 (4.8)	26.7 (4.5)	0.88	0.49	0.31	0.06	0.52
Smoking status, %					0.004	<0.0001	0.009	0.59	0.0002
Active smoker	301 (29.7%)	32 (49.2%)	14 (17.9%)	58 (22.1%)					
Former smoker	433 (42.8%)	20 (30.8%)	31 (39.7%)	90 (34.2%)					
Never smoker	278 (27.5%)	13 (20%)	33 (42.3%)	115 (43.7%)					
Packs-year, mean (SD)	29.2 (30.1)	22.2 (21.35)	18.5 (25.6)	13.1 (17.9)	0.06	0.0005	0.002	0.04	0.35
Education level, %					0.15	0.03	0.23	0.27	0.56
No studies	41 (4.1%)	0	1 (1.3%)	2 (0.8%)					
Primary education	270 (26.7%)	14 (21.5%)	17 (21.8%)	52 (19.8%)					
Secondary education	243 (24.0%)	19 (29.3%)	17 (21.8%)	45 (17.1%)					
University or vocational training	454 (44.9%)	31 (47.7%)	42 (53.8%)	164 (62.4%)					

	COPD (C) (n=1012)	Young COPD (YC) (n=65)	Pre-COPD (PC) (n=78)	Non-COPD (NC) (n=263)	P value				
					C versus YC	NC versus YC	C versus PC	NC versus PC	PC versus YC
Clinical characteristics									
MMRC dyspnea scale, %					0.14	0.0009	0.32	<0.0001	0.01
Grade 0	499 (49.2%)	42 (64.6%)	30 (38.5%)	223 (84.8%)					
Grade 1	355 (35.1%)	18 (27.7%)	36 (46.2%)	36 (13.7%)					
Grade 2	113 (11.2%)	3 (4.6%)	9 (11.5%)	3 (1.1%)					
Grade 3	39 (3.9%)	2 (3.1%)	3 (3.8%)	1 (0.4%)					
Grade 4	6 (0.6%)	0	0	0					
CAT, mean (SD)	9.1 (6.8)	9.1 (6.4)	11.3 (6.1)	5.7 (5.1)	0.98	<0.0001	0.004	<0.0001	0.03
Cough and phlegm (CECA questionnaire), %	621 (66.3%)	37 (58.7%)	78 (100.0%)	70 (28.0%)	0.21	<0.0001	<0.0001	<0.0001	<0.0001
Asthma, %	163 (16.1%)	19 (29.2%)	5 (6.4%)	24 (9.1%)	0.006	<0.0001	0.02	0.45	0.0003
Charlson Comorbidity Index, mean (SD)	0.7 (1.1)	0.6 (1.7)	0.5 (0.9)	0.3 (0.8)	0.71	0.01	0.22	0.01	0.63
COTE Index, mean (SD)	1.2 (2.4)	1.4 (2.8)	1.7 (2.8)	0.9 (2.1)	0.44	0.12	0.10	0.01	0.62
Exacerbations last year, %	114 (11.3%)	5 (7.7%)	2 (2.6%)	9 (3.4%)	0.37	0.12	0.01	0.70	0.15
Treatments									
Any respiratory treatment, %	641 (63.3%)	28 (43.1%)	39 (50.0%)	86 (32.7%)	0.001	0.11	0.01	0.005	0.40
Treatment with short-acting beta-agonist, %	251 (24.8%)	17 (26.2%)	4 (5.1%)	8 (3.0%)	0.80	<0.0001	<0.0001	0.37	0.0004
Treatment with anticholinergics, %	159 (15.7%)	4 (6.2%)	2 (2.6%)	5 (1.9%)	0.03	0.06	0.001	0.71	0.28
Treatment with inhaled	189 (18.7%)	10 (15.4%)	4 (5.1%)	9 (3.4%)	0.50	0.0002	0.002	0.48	0.03

	COPD (C) (n=1012)	Young COPD (YC) (n=65)	Pre-COPD (PC) (n=78)	Non-COPD (NC) (n=263)	P value				
					C versus YC	NC versus YC	C versus PC	NC versus PC	PC versus YC
corticosteroids, %									

SD: Standard deviation; P25: 25th percentile; P75: 75th percentile
BMI: Body Mass Index; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in the first second; MMRC: Modified Medical Research Council Dyspnea Scale; CAT: COPD Assessment Test; CECA questionnaire: European Coal and Steel Community (from Spanish); DLCO: Diffusing Capacity of the Lungs for Carbon Monoxide; CRP: C-Reactive Protein

Table 2: Differential functional, inflammatory and imaging characteristics of Young and Pre-COPD subjects compared to COPD and non-COPD populations.

	COPD (C) (n=1012)	Young COPD (YC) (n=65)	Pre-COPD (PC) (n=78)	Non-COPD (NC) (n=263)	P value				
					C versus YC	NC versus YC	C versus PC	NC versus PC	PC versus YC
Lung function									
FVC (%), mean (SD)	99.3 (18.5)	99.8 (14.8)	101.2 (16.5)	104.9 (13.3)	0.83	0.02	0.39	0.11	0.60
FEV_1 (%), mean (SD)	80.6 (18.8)	80.3 (16.2)	103.6 (18.0)	105.3 (13.7)	0.08	<0.0001	<0.0001	0.33	<0.0001
6 MWT, mean (SD)	477.1 (108.1)	525.5 (121.0)	467.3.0 (114.8)	527.2 (87.8)	0.09	0.94	0.47	<0.0001	0.07
DLCO (%), mean (SD)	88.6 (23.1)	108.9 (19.5)	90.9 (19.4)	101.5 (17.4)	0.001	0.11	0.40	<0.0001	0.001
BODE Index (0-10), mean (SD)	1.5 (1.2)	1.1 (0.8)	1.4 (0.9)	0.9 (0.4)	0.13	0.30	0.24	<0.0001	0.22
BODEx Index (0-9), mean (SD)	1.4 (1.0)	1.3 (0.9)	1.2 (0.6)	0.9 (0.3)	0.19	<0.0001	0.01	<0.0001	0.31
Biomarkers									
Eosinophils, mean (SD) (median (P25;P75))	191 (123) 175 (101 ; 249)	233 (169) 182 (168 ; 227)	158 (95) 140 (89 ; 215)	159 (120) 128 (88 ; 198)	0.22	0.02	0.03	0.98	0.02
CRP (mg/dL), mean (SD)	1.9 (4.0)	2.1 (4.1)	1.6 (2.8)	1.3 (2.7)	0.93	0.33	0.46	0.43	0.60

	COPD (C) (n=1012)	Young COPD (YC) (n=65)	Pre-COPD (PC) (n=78)	Non-COPD (NC) (n=263)	P value				
					C versus YC	NC versus YC	C versus PC	NC versus PC	PC versus YC
(median (P25;P75))	0.4 (0.1 ; 2.0)	0.2 (0.1 ; 1.0)	0.6 (0.1 ; 1.5)	0.4 (0.1 ; 1.1)					
Fibrinogen (g/L) , mean (SD)	3.9 (0.9)	3.3 (0.8)	3.9 (1.1)	3.7 (0.8)	0.02	0.07	0.995	0.10	0.04
(median (P25;P75))	3.7 (3.3 ; 4.5)	3.0 (2.7 ; 4.0)	3.9 (3.2 ; 4.5)	3.6 (3.1 ; 4.3)					
Imaging									
Emphysema >5%, %	160 (59.7%)	3 (27.3%)	39 (50.0%)	55 (20.9%)	0.03	0.61	0.12	<0.0001	0.15
Airway Thickness Bronchiole					0.67	0.21	0.03	0.0001	0.69
[mm], mean (SD)	1.1 (0.1)	1.1 (0.1)	1.1 (0.2)	1.0 (0.2)					
(median (P25;P75))	1.1 (1.0 ; 1.1)	1.1 (1.1 ; 1.2)	1.1 (1.0 ; 1.2)	1.1 (1.0 ; 1.1)					

SD: Standard deviation; P25: 25th percentile; P75: 75th percentile

BMI: Body Mass Index; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in 1 second; MMRC: Modified Medical Research Council Dyspnea Scale; CAT: COPD Assessment Test; 6 MWT: 6-min walk test;

COTE: Copd cO-morbidity Test; BODE: BMI, Obstruction, Dyspnea, Exercise (BODE) index; DLCO: Diffusing Capacity of the Lungs for Carbon Monoxide

Figure legends

Figure 1. Flowchart of participants included in the analysis

Figure 2. Proportional Venn diagram of COPD traits sub-populations

Figure 3. Differential clinical characteristics among subjects classified as Young COPD (n=65), pre-COPD (n=78) compared to COPD (n=1012) and non-COPD (n=263) in the general population. Data on clinical characteristics were collected in >95% of individuals per group. “Exacerbations last year” accounts for at least one exacerbation requiring antibiotic or oral steroid or emergency visit in the previous 12 months.

Figure 1

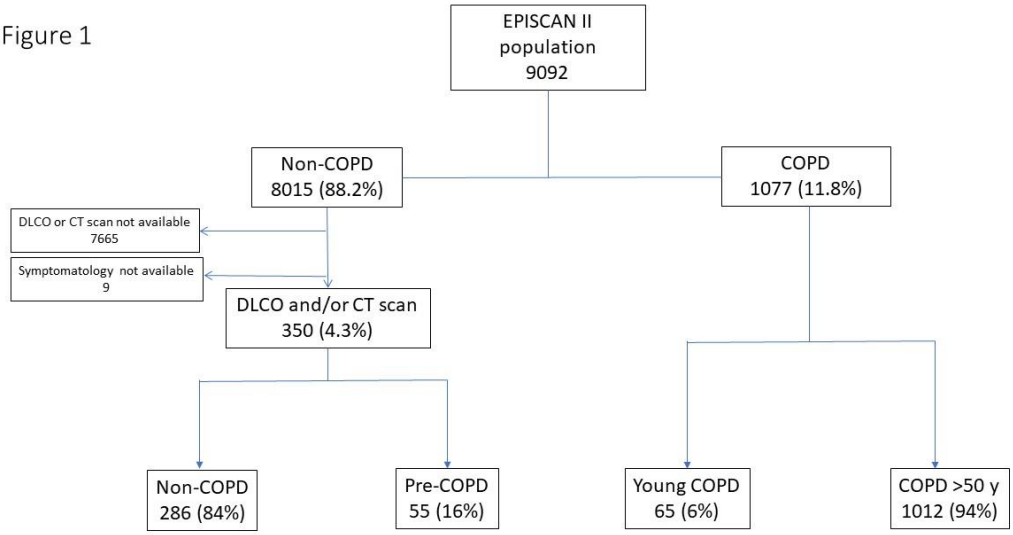

EPISCAN II
population
9092
Non-COPD
8015 (88.2%)
COPD
1077 (11.8%)
DLCO or CT scan not available
7665
Symptomatology not available
9
DLCO and/or CT scan
350 (4.3%)
Non-COPD
286 (84%)
Pre-COPD
55 (16%)
Young COPD
65 (6%)
COPD >50 y
1012 (94%)

Figure 2

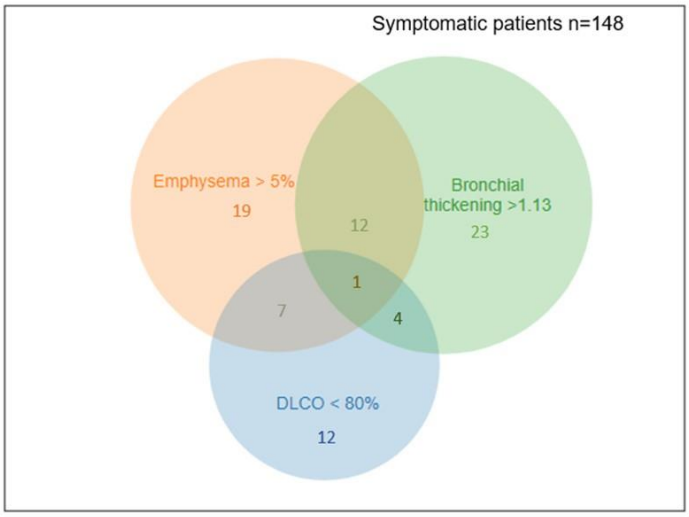
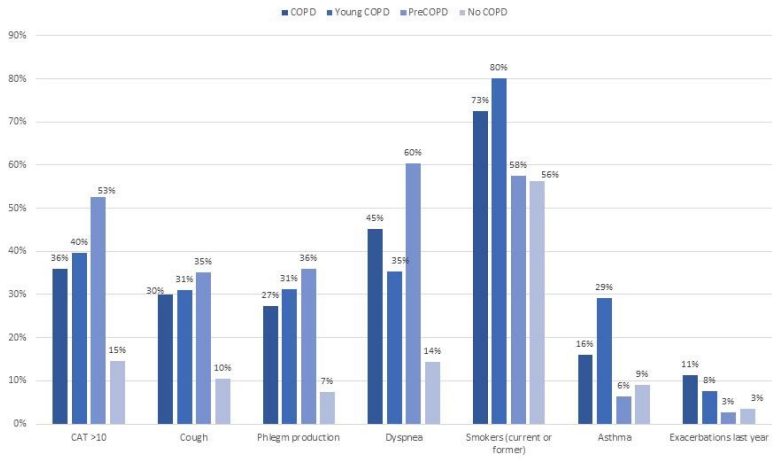

Symptomatic patients n=148
Emphysema > 5%
19
Bronchial thickening >1.13
23
DLCO < 80%
12
12
1
7
4

Figure 3


COPD
Young COPD
PreCOPD
No COPD
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
36%
40%
53%
15%
30%
31%
35%
10%
27%
31%
36%
7%
45%
35%
60%
14%
73%
80%
58%
56%
16%
29%
6%
9%
11%
8%
3%
3%
CAT >10
Cough
Phlegm production
Dyspnea
Smokers (current or former)
Asthma
Exacerbations last year

APPENDIX

Principal Investigators, collaborators, and participating centres:

Autonomous Community	**CENTRE**	**INVESTIGATOR TEAM**
MADRID	H. La Princesa	Julio Ancochea Bermudez (IP) / Elena García Castillo / Claudia Valenzuela / Joan B Soriano
CASTILLA LEÓN	H. U. de Burgos	Ana Pueyo Bastida (IP) / Lourdes Lázaro Asegurado / Luis Rodríguez Pascual / Mª José Mora
ARAGÓN	H. Gral. San Jorge	Luis Borderias Clau (IP) / Lourdes Arizón Mendoza / Sandra García
EXTREMADURA	H. San Pedro de Alcántara	Juan Antonio Riesco Miranda (IP) / Julián Grande Gutiérrez / Jesús Agustín Manzano / Manuel Agustín Sojo González
CASTILLA LEÓN	H. Clínico U. de Salamanca	Miguel Barrueco Ferrero (IP) / Milagros Rosales
GALICIA	H. Álvaro Cunqueiro	José Alberto Fernández Villar (IP) / Cristina Represas / Ana Priegue / Isabel Portela Ferreño / Cecilia Mouronte Roibás / Sara Fernández García
I. BALEARES	H. Son Espases	Borja G Cosío (IP) / Rocío Cordova Díaz / Nuria Toledo Pons / Margalida Llabrés
ARAGÓN	H. U. Miguel Servet	José María Marín Trigo (IP) / Marta Forner / Begoña Gallego / Pablo Cubero / Elisabet Vera
C. VALENCIANA	H. Arnau de Vilanova (Valencia)	Juan José Soler Cataluña (IP) / Mª Begoña Picurelli Albero / Noelia González García
ANDALUCÍA	H. Virgen de la Macarena	Agustín Valido Morales (IP) / Carolina Panadero / Cristina Benito Bernáldez/ Laura Martín -Bejarano y Maria Velarde

MURCIA	H. Gral. U. Santa Lucía (Cartagena)	Antonio Santa Cruz Siminiani (IP) / Carlos Castillo Quintanilla / Rocío Ibáñez Meléndez / José Javier Martínez Garcerán / Desirée Lozano Vicente / Pedro García Torres / Maria del Mar Valdivia
NAVARRA	Clínica Universidad de Navarra	Juan Pablo de Torres Tajes (IP) / Montserrat Cizur Girones / Carmen Labiano Turrillas
LA RIOJA	H. de San Pedro (Logroño)	Carlos Ruiz Martínez (IP)/ Elena Hernando / Elvira Alfaro / José Manuel García / Jorge Lázaro
PAÍS VASCO	H. Santiago Apóstol (H. Txagorritxu)	David Bravo (IP) /Laura Hidalgo / Silvia Francisco Terreros / Iñaki Zorrilla / Ainara Alonso Colmenero /
ASTURIAS	H. Central de Asturias	Cristina Martínez González (IP) /Susana Margon/ Rosirys Guzman Taveras/ Ramón Fernández / Alicia Álvarez
CANTABRIA	H. de Valdecilla (Servicio de Neumología en el H. Santa Cruz de Liencres)	José Ramón Agüero Balbín (IP) / Juan Agüero Calvo
CATALUÑA	H. U. Vall d'Hebron	Jaume Ferrer Sancho (IP) / Esther Rodríguez González/ Eduardo Loeb
CASTILLA LA MANCHA	H. U. de Guadalajara	José Luis Izquierdo Alonso (IP) / Mª Antonia Rodríguez García
I. CANARIAS	H. U. de Tenerife	Juan Abreu González (IP)/ Candelaria Martín García/ Rebeca Muñoz/ Haydée Martín García
ASTURIAS	H. U. de San Agustín (Avilés):	Miguel Angel Martínez Muñiz (IP) / Andrés Avelino Sánchez Antuña / Jesús Allende González / Jose Antonio Gullón Blanco / Fernando José Alvarez Navascues / Manuel Angel Villanueva Montes / María Rodríguez Pericacho / Concepción Rodríguez García / Juan Diego Alvarez Mavárez