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The EPI-SCAN Survey to Assess the Prevalence of Chronic Obstructive Pulmonary Disease in Spanish 40-to-80-Year-Olds: Protocol Summary

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ABSTRACT

Background and Objectives. Chronic obstructive pulmonary disease (COPD) causes considerable morbidity and mortality in Spain. The 1997 IBERPOC study, applying the old criteria of the European Respiratory Society, reported a COPD prevalence of 9.1% in the adult population of Spain. The Epidemiologic Study of COPD in Spain (EPI-SCAN) aims to determine the current prevalence of COPD in residents of Spain aged 40 to 80 years. Secondary objectives are, among others, to describe the current prevalence of smoking and changes in COPD prevalence relative to previous studies; to describe treatments received by patients, quality of life, and the BODE index (body mass index, obstruction of airflow, dyspnea, and exercise tolerance); and to measure inflammatory markers in blood and exhaled-breath condensate.
Patients and Methods. EPI-SCAN is a population-based, cross-sectional epidemiologic study targeting the general population of Spain aged between 40 and 80 years. Participating centers were located in Barcelona, Burgos, Cordoba, Huesca, Madrid, Oviedo, Seville, Valencia, Vic, and Vigo. All subjects filled in an extensive questionnaire to collect social, demographic, and clinical information. Slow and forced spirometry tests before and after a bronchodilator test were also undertaken. Additionally, selected subjects performed a 6-minute walk test and answered generic and specific quality-of-life questionnaires, as well as an activities-of-daily-living questionnaire. Exhaled-breath condensate and blood samples were also collected from these subjects for measurement of inflammatory and other biomarkers.

Palabras clave:
Epidemiología
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Estudio EPI-SCAN: resumen del protocolo de un estudio para estimar la prevalencia de EPOC en personas de 40 a 80 años en España

RESUMEN

Introducción y objetivos. La enfermedad pulmonar obstructiva crónica (EPOC) es un trastorno que causa gran morbilidad y mortalidad en España. El estudio IBERPOC, realizado en 1997, identificó una prevalencia de EPOC en España, según el criterio antiguo de la European Respiratory Society, del 9,1% de la población adulta. El estudio EPI-SCAN (del inglés *The Epidemiologic Study of COPD in Spain*) pretende conocer la prevalencia de la EPOC en población de 40 a 80 años de edad residente en España en la actualidad y sus cambios en el último decenio. Otros objetivos secundarios que se plantean son describir la prevalencia de tabaquismo, la evolución de la prevalencia de EPOC respecto a estudios previos, el tratamiento recibido por los pa-

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cientes, la calidad de vida y el índice BODE (índice de masa corporal, obstrucción al flujo aéreo, disnea y capacidad de ejercicio), y determinar marcadores inflamatorios en sangre y en condensado exhalado.
Pacientes y método. EPI-SCAN es un estudio epidemiológico de base poblacional, transversal, de ámbito nacional, llevado a cabo en población general de 40 a 80 años residente en España. Las áreas participantes fueron: Barcelona, Burgos, Córdoba, Huesca, Madrid, Oviedo, Sevilla, Valencia, Vic y Vigo. Todos los participantes rellenaron un cuestionario sociodemográfico y clínico extenso, y realizaron una espirometría lenta y forzada antes y después de una prueba broncodilatadora. Además, algunos participantes seleccionados efectuaron las siguientes pruebas: prueba de la marcha de 6 min, medición de la calidad de vida mediante cuestionarios específico y genérico, y de actividades de la vida diaria, recogida del condensado de aire exhalado y obtención de una muestra de sangre para medición de biomarcadores y diferentes parámetros inflamatorios.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide,[1] even though relatively few studies have described its prevalence.[2]

The epidemiology and distribution of this disease in the general population internationally, and in Spain in particular, are still points on which relatively little is known.[3] Several population-based surveys have been carried out in Spain and were recently reviewed.[4] The IBERPOC epidemiologic study of COPD in Spain,[5,6] which was undertaken by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), was unquestionably the most important population-based survey in the country. Its study design has served as a model for later international projects.[7,8]

Notwithstanding the considerable contributions these earlier studies made to our understanding of the distribution of COPD in the population, prevalence rates must be regularly updated. Epidemiology, the study of the distribution of health events and states in populations, assumes that prevalence will vary if the contributing factors change at a particular location or over time.[9] As is the case for other chronic smoking-related diseases, the distribution of COPD depends mainly on 2 factors: accumulated exposure and gradual population aging. Spain unfortunately leads Europe in smoking among adolescents[10] and is also among the countries with the highest rates of female smokers worldwide.[11] It was against this background that we designed the Epidemiologic Study of COPD in Spain (EPI-SCAN) with the aim of estimating the prevalence of the disease in residents of Spain aged 40 to 80 years. In addition, a set of secondary objectives have been set to look at trends, risk factors, diagnostic variables, and reference values (Table 1). This paper summarizes the EPI-SCAN study protocol.

Table 1
The EPI-SCAN Objectives

Main objective:
To estimate the population prevalence of COPD in residents of Spain aged 40 to 80 years
Secondary objectives:
To describe the current population prevalence of smoking in residents of Spain aged 40 to 80 years, according to sex
To describe COPD prevalence according to levels of severity
To describe changes in COPD prevalence relative to previous studies
To obtain reference values for the 6-minute walk test and inflammatory markers in a healthy population
To assess health-related quality of life
To compare the 3 study cohorts in terms of inflammatory markers, and scores on the London Chest Activity of Daily Living questionnaire and an occupational exposure questionnaire
To compare COPD prevalence by level of severity in terms of diverse diagnostic criteria
To carry out a multidimensional COPD assessment using the BODE index (body mass index, obstruction of airways, dyspnea, and exercise tolerance)
To evaluate whether treatment received by patients with COPD of different levels of severity complies with international guidelines
To determine the reliability and reproducibility of measures performed on exhaled-breath condensate samples

Patients and Method

Design

EPI-SCAN is a multicenter, epidemiologic, observational, population-based cross-sectional survey carried out on a Spanish national level. Participants were selected with a 2-phase sampling method in which the population was stratified by areas near participating centers in 4 parts of Spain (the northern, Mediterranean coastal, southern, and central regions of the country). The participating centers are in the following cities: Barcelona, Burgos, Cordoba, Huesca, Madrid, Oviedo, Seville, Valencia, Vic, and Vigo.

Targeted for inclusion were men or women resident in Spain and aged 40 to 80 years. All participants were interviewed in a short visit as defined in the design of the study (Figure). The population was then divided into 3 cohorts according to spirometry and responses to questions about previously defined variables based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifications in use during the design phase of the study[12]: *a)* diagnosed COPD (GOLD I-IV), individuals with a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) that was less than 0.70 after a bronchodilator test; *b)* GOLD 0; and *c)* no evidence of COPD. The last group was subdivided into those reporting no respiratory symptoms, who answered negatively to all questions about such symptoms in the questionnaire of the European Coal and Steel Community (ECSC)[13] (Table 2), and those who did report respiratory symptoms. It must be noted that after the study had started, the GOLD classification ceased to include a GOLD 0 category.[1] However, we believe that the results of the EPI-SCAN study will be able to

Table 2
Descriptions of the Study Cohorts

Cohort 1: COPD (GOLD I-IV)
FEV_1/FVC <0.70 after a bronchodilator test
Cohort 2: GOLD 0
FEV_1/FVC ≥0.70 after a bronchodilator test (criterion 26, ECSC questionnaire)
Current or ex-smokers of 10 pack-years
Cough and/or sputum production at least 3 months in the last year (criteria 3 and/or 7, ECSC questionnaire)
Cohort 3: No COPD
Individuals without symptoms reported on the ECSC questionnaire
FEV_1/FVC ≥0.70 after a bronchodilator test (criterion 26, ECSC questionnaire)
Negative ECSC questionnaire (no to all questions)
Individuals reporting respiratory symptoms on the ECSC questionnaire
Individual who could not be classified in any group

Abbreviations: ECSC, European Coal and Steel Community; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, classification of the Global Initiative for Chronic Obstructive Lung Disease.

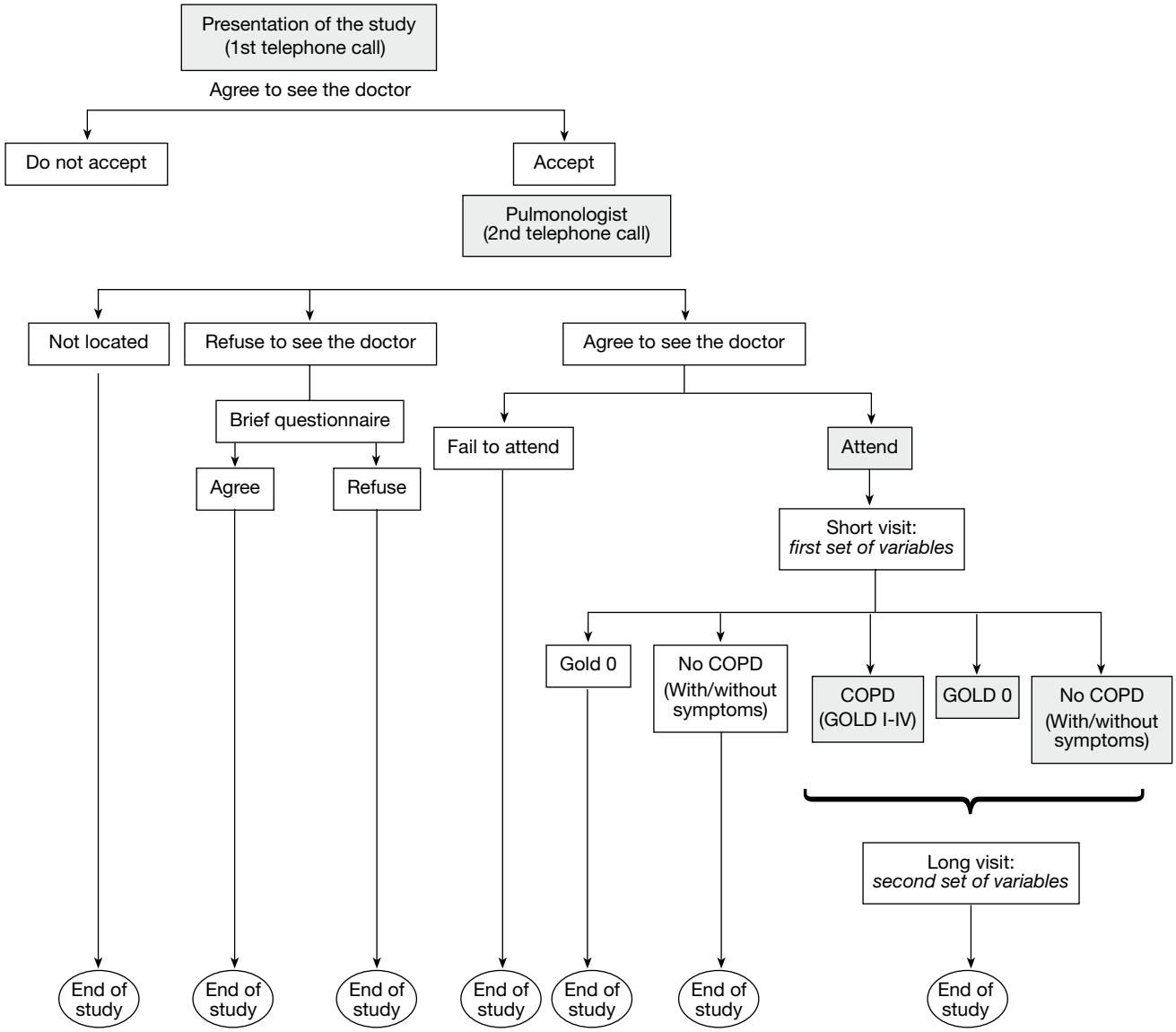

Figure. Study Design. For each COPD patient who attended a long visit, an equivalent long visit was also carried out with an individual with a classification of 0 according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) or with a healthy participant (no COPD).

provide support for the new GOLD classifications or allow their further revision based on a higher level of evidence.

All participants with COPD who were identified in the short visit were also interviewed during a long visit at which the remaining study data (secondary variables) were collected. Additionally, an equal number of participants from the GOLD 0 or no-COPD cohorts were studied at each center. These subjects were selected consecutively, without alternation, until the study ended. The long interview was not conducted with all participants, according to study design, so as not to perform excessive testing of the study population without COPD (Figure). The study was approved by the corresponding research ethics committees. The committee of reference was that of Hospital Clínic i Provincial de Barcelona. All participants voluntarily signed a statement expressing their consent to testing.

Participant Selection

Random sampling took place in 2 phases and was population-based, carried out by means of a random telephone survey. Before sampling, the postal codes nearest each hospital were determined to define the participating areas. In the first phase, we used a random list of telephone numbers stratified by postal code. In the second phase, trained staff belonging to a specialized company made the first screening calls by means of a system for computer-assisted telephone interviewing. This call provided information about the study and asked the individual to consent to receiving a second call, during which the researcher sought to arrange an appointment for a clinical interview at the hospital. Persons who did not agree to an appointment were administered a brief questionnaire covering sociodemographic variables and respiratory symptoms and diagnoses. The participants who did attend the hospital visit made up the study sample.

Study Organization

Two epidemiologists and 6 respiratory medicine specialists formed a scientific advisory committee to prepare the study and serve as consultants (Appendix). The field work was carried out

from May 2006 through July 2007 at 11 centers. Each participating hospital assigned a pulmonologist as coordinator, from 1 to 3 pulmonologists or other appropriately trained physicians as principal researchers, and a nurse charged with obtaining and processing samples.

Variables and Procedures

Questionnaires. Once a participant agreed to be interviewed by a pulmonologist, a hospital appointment was made for the short visit. At this visit, the physician collected the first set of data, concerning social and demographic information, smoking habits, diagnoses of respiratory or other diseases, exacerbations, dyspnea, treatments taken for respiratory diseases, details of respiratory symptoms (ECSC questionnaire), and information related to occupational exposure. The instruments used and measures taken at this time are described below.

We used a validated Spanish translation[13] of the original English-language ECSC questionnaire. The Spanish questionnaire has 26 items in 6 sections, covering cough and sputum production, dyspnea, wheezing and chest tightness, and asthma attacks and treatments (inhaled, rectal, oral, or injected). This is the standard questionnaire used in population-based studies of the prevalence of chronic respiratory symptoms in adults. The answers given allow the researcher to gain an approximate picture of a range of situations, such as chronic cough, chronic sputum production or dyspnea. Severity can also be estimated and chronic bronchitis distinguished.

The modified scale of the Medical Research Council (mMRC)[14] was used to characterize dyspnea. This scale asks the participant to give a subjective rating of dyspnea at certain levels of effort during everyday activities, from grade 1, "shortness of breath when hurrying on the level or walking up a slight hill" (or, backtranslated literally from the Spanish version, "dyspnea only with strenuous exercise"), to grade 5, "breathless when dressing or undressing" (or, backtranslated from the Spanish version, "breathless at rest or while carrying out activities of daily living").

For the entire sample and for the group of COPD-diagnosed patients, respiratory therapy was registered according to the following pharmacologic groupings: bronchodilators, inhaled anti-inflammatory drugs, other treatments (eg, vaccines, antibiotics, mucolytic agents), and oxygen therapy.

The London Chest Activity of Daily Living (LCADL) scale[15] was used to score this aspect. This specific questionnaire has 15 items in 4 activity groups: personal care (4 items), domestic tasks (6 items), physical exercise (2 items), and leisure activity (3 items). For each activity named, shortness of breath is rated on a scale of 0 to 5, generating a score for each activity group and a total score. The Spanish translation of the LCADL questionnaire has been validated.[16] Finally, 2 quality-of-life questionnaires were used, as follows: the EQ-5D questionnaire of the EuroQol group[17,18] and the St George's Respiratory Questionnaire (SGRQ).[19] The EQ-5D is a short, generic quality-of-life assessment tool with scores obtained on the basis of a section asking for responses to a description, followed by a section with a visual analog scale for self-assessment of overall health status. The section using the descriptive system covers 5 dimensions (mobility, personal care, daily activities, pain/discomfort, and anxiety/depression) and asks the respondent to rate themselves according to 3 options ranging from free of problems to having moderate or serious problems. Then, a visual analog scale is presented as a thermometer with the lowest (0) and highest (100) scores labeled as worst (0) and best (100) imaginable health states, respectively. The SGRQ[19] is a specific quality-of-life questionnaire with 50 items in 3 dimensions: symptoms (8 items), activities (16 items), and impact on daily living (26 items). Responses for symptoms are given on a Likert-type scale and the others are answered with yes or no. An overall score and scores for each dimension are given. Low scores indicate better quality of life. The EPI-SCAN survey used a validated Spanish version adapted for use in Spain.[20]

Spirometry. Both slow and forced spirometry were performed in all centers with the same equipment (Master Scope CT, VIASYS Healthcare, Hoechberg, Germany). Criteria for acceptability and reproducibility of measurements and for selection of the maneuver to record as valid were those recommended most recently by the American Thoracic Society (ATS) and the European Respiratory Society (ERS).[21] European reference values were used.[22] Slow and forced maneuvers were repeated 15 to 30 minutes after inhalation of 200 μg of salbutamol. Following the ATS/ERS criteria,[23] a bronchodilator test was considered positive when an increase of more than 200 mL and 12% of baseline was observed in FVC or FEV_1.

As a quality assurance measure, we analyzed the first 1745 procedures performed in all centers. This analysis verified that 89.1% of all maneuvers began properly (with a back-extrapolated volume of <150 mL or 5% of FVC), that 85.6% of the maneuvers had a duration of at least 6 seconds, and that 90.6% had a satisfactory end-expiratory plateau (volume change <30 mL in the last second). Overall, 80.3% of the maneuvers were acceptable. It was also seen that 95.3% of spirometries complied with the ATS criteria[24] for FEV_1 reproducibility; 96.4% met the standards for FVC reproducibility.

Other measures. The long visit was completed by all participants assigned to the COPD cohort and an equal number of consecutively selected participants from the GOLD 0 cohort and the cohort of participants without COPD (with and without symptoms according to the ECSC questionnaire). At that time, pulse oximetry and the distance covered in a 6-minute walk test were noted, and blood and exhaled-breath condensate samples were collected.

–*Walk test***.** ATS guidelines for the 6-minute walk test were followed.[25] Researchers were given instructions to follow in order to perform the test in the correct, standardized way. To control for the learning effect, 2 walks were performed with a 30-minute rest between them. If the participant was highly symptomatic in the first walk, whether or not to perform the second was left to the discretion of the treating physician.

–*Exhaled-breath condensate***.** Only 2 of the centers (Hospital Clínic i Provincial de Barcelona and Hospital La Paz in Madrid) had the means to collect exhaled-breath condensate samples. After estimating the number of such samples needed in order to draw conclusions without overburdening the participants with tests, it was decided to collect 44 samples.

–*Blood samples***.** In the long visit, 20 mL of blood was extracted from each participant to determine levels of α_1-antitrypsin, C-reactive protein, tumor growth factor α, interleukin (IL) 6 and 8, fibrinogen, albumin, nitrites, and nitrates. Standardized procedures were used for collecting both blood and exhaled-breath condensate samples. Each center was required to store samples at –80°C. Samples were sent to the laboratory at Hospital Clínic i Provincial de Barcelona for centralized analysis approximately every 2 months. That laboratory provided the nurse at each center with a manual describing how to extract and store the samples according to protocol. In order to select healthy participants for the walk test and for blood sampling to determine inflammatory markers, the exclusion criteria shown in Table 3 were taken into consideration.

Data Collection

Data were collected by means of a specially designed website (http://episcan.hor-europe.com/frmValida.asp). Researchers could access the random sample of telephone numbers to call and fields were provided for entering data.

After the interviewers obtained informed consent from the participants, the study variables were recorded on paper in a notebook. These data were regularly transferred to the database.

Table 3
Exclusion Criteria for Performance of the Walk Test and Measurement of Inflammatory Markers

Walk Test	Inflammatory Markers
Unstable angina in the last month	Acute myocardial infarction or angina
Acute myocardial infarction in the last month	Congestive heart failure
Resting heart rate >120 beats/min	Neoplasm
Systolic blood pressure >180 mm Hg	Hepatic cirrhosis
Diastolic blood pressure >100 mm Hg	Chronic renal failure
	Rheumatoid arthritis
	Systemic inflammatory disease with elevated C-reactive protein levels

Short visits (to obtain the first dataset) lasted 1 hour. Long visits (to collect data for the first and second datasets) lasted 2.5 to 3 hours.

Sample Size Calculation

The sample size was estimated on the basis of a COPD prevalence of 12% (precision, ±1%). Assuming losses of 20%, it was decided that the number of individuals theoretically required to enroll in the study would be 5071. At least 486 individuals with COPD would be needed. Estimating a prevalence of 20% for individuals with GOLD 0 classification,[26] it was calculated that this group should consist of 811 participants and that the remaining 2759 should belong to the population sample without COPD.

Statistical Analysis

For continuous variables, results are to be expressed as mean (SD), median, range, and the number of valid cases. Categorical variables will be expressed as the number of cases in each category and the relative frequency of the total number of responses. Data will be analyzed using the SPSS statistical package, version 15 (SPSS Inc, Chicago, Illinois, USA) for Windows. The level of significance will be a value of *P* less than .05 in all statistical tests.

Nonresponse bias will be explored by comparing the social, demographic, and clinical characteristics of study participants to those of individuals who did not consent to participate.

The prevalence of COPD and the 95% confidence interval will be calculated according to spirometry criteria (old ERS, old ATS, and GOLD criteria). Agreement between diagnostic criteria will be estimated by means of the percentage of cases with the same classification and by the κ index. To determine the risk of developing COPD by gender, age, and other potentially relevant variables, multivariate logistic regression analysis will be used. The dependent variable will be presence of COPD. Independent variables will be age, sex, and the other factors that might be related to this disease.

Descriptive statistics will be compiled for the social and demographic characteristics (sex, age, educational level, occupation, smoking) and clinical characteristics (prior diagnosis of asthma, other respiratory diagnoses, concomitant diseases, spirometry history, exacerbation history, symptoms suggestive of COPD). Also described will be the anthropometric characteristics of the study population (weight, height, body mass index), the mMRC dyspnea score, the results of the battery of tests (pulse oximetry, slow and forced spirometry after a bronchodilation test, laboratory findings for blood and exhaled-breath condensate samples, walk test distance), symptoms (ECSC questionnaire), and occupational exposure. The index of participants with COPD will be determined.[27]

Social, demographic, and clinical data will be compared between the 3 study cohorts (GOLD I-IV, GOLD 0, and subjects without COPD). In situations determined to be of interest, the cohort without COPD will be divided according to whether symptoms are or are not reported on the ECSC questionnaire. Comparisons will be performed with the *t* test or analysis of variance (ANOVA), as appropriate, for continuous variables, and with the χ^2 test for categorical variables. If ANOVA demonstrates that *P* is less than .05, to guard against the appearance of significance in multiple comparisons, a Bonferroni post-hoc test will be performed to detect differences in 2-by-2 analyses, with a significance threshold set at .01.

Discussion

The EPI-SCAN survey should allow us to determine changes in the epidemiologic situation for COPD in Spain. The most representative data available at this time are from the IBERPOC study, whose field work was carried out over 10 years ago.[5]

That study was designed to measure prevalence and detect variation in the distribution of COPD across Spain. Seven geographic areas (Burgos, Caceres, Madrid, Manlleu, Oviedo, Seville, and Vizcaya) were identified and the population aged 40 to 69 years was sampled randomly from census records. The prevalence of COPD (defined according to the old ERS criteria[28] by a ratio of FEV_1/FVC <88% of predicted for men and <89% for women) was 9.1% in 1997 (in men, 14.3%; in women, 3.9%). Stratification of the population by smoking habit showed that the prevalence of COPD was 15% in smokers, 12.8% in ex-smokers, and 4.1% in never smokers.[29] That study also found large differences by geographic area, with rates ranging from as low as 4.9% in Caceres to as high as 18% in Manlleu. Such differences may have been related to environmental or occupational factors that were not studied. An important finding was the high degree of underdiagnosis: 78.2% of COPD cases confirmed by spirometry were found in previously undiagnosed patients. Other observations of note were an independent association between a diagnosis of COPD and urban residence, male gender, older age, low socioeconomic status, smoking history, and a history of chronic bronchitis.[30] IBERPOC estimated that 1 228 000 individuals aged between 40 and 69 years in Spain had COPD and that 75% had not been diagnosed.[29]

Other Spanish studies have calculated COPD prevalence rates that are very similar to those of the IBERPOC study. One such study was carried out in the Catalan county of Valles in a population sampled from census records for adults aged 20 to 70 years.[31] Applying the criteria of the British Thoracic Society,[32] the authors found the prevalence of airflow limitation (FEV_1 <80% and FEV_1/FVC <0.7) to be 7.2% in the population overall, 10.4% in men, and 4.1% in women. Those rates were higher at older ages and in smokers and ex-smokers. Local population-based studies in Valencia,[33] Guipuzcoa,[34] and Castellon[35] reported very similar prevalences. Another study, carried out in the province of Toledo in the population of smokers or ex-smokers aged more than 40 years, calculated a prevalence of 16.4% (95% confidence interval, 12.9-19.9).[36] However, direct comparisons of prevalences in different studies, even for the same geographic areas, are problematic and should be attempted with caution. Thresholds chosen for diagnosis and severity classifications may vary,[37] and there may be subtle differences in protocols for inclusion and exclusion, number of attempts during forced spirometry, or variations in the dosages, duration, or drug used for spirometry after a bronchodilator test.[38]

According to the latest available data from the 2007 Spanish National Health Survey,[39] 27.1% of the adult population smokes and the percentage in men (32.2%) is higher than in women (22.1%). Although the rate for men is slightly lower than it was in the 1990s, there has been no decrease in the prevalence for women. As Spanish population growth is expected to peak in 2050, when there will be 53 million inhabitants, and the mean age will be at its highest around 2060,[40] we can foresee a consequent increase in the population at risk of developing irreversible airflow limitation. For these reasons, it is likely that the coming years will see a national COPD epidemic,

defined as a higher number of cases than expected in a given space and time. Following trends in risk factors and compiling new epidemiologic data on COPD should therefore be considered a national priority.

Finally, it should be emphasized that the design of the EPI-SCAN study is unique, given the biological samples obtained randomly from a population-based sample. This should allow the investigation of variables that may be related to susceptibility to or prognosis of COPD. It will be of particular interest to see if participants in the former GOLD 0 classification[12] present distinct biochemical characteristics and a different clinical phenotype in comparison with asymptomatic smokers, and if these data can contribute a new perspective on the classification of patients with symptoms but without airflow limitation.

In formulating the EPI-SCAN protocol, it was decided to give priority to using European reference values[22] in order to encourage wider projection of results. However, as absolute values were also recorded, it will also be possible to present the results in terms of Spanish[41] or other reference values.

The EPI-SCAN survey also sets out to meet a set of secondary objectives that will allow us to describe trends and variables of interest, stratifying the population by levels of COPD severity (Table 1), at the same time the prevalence of the disease in residents of Spain aged 40 to 80 years is being established.

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Appendix

Members of the scientific advisory committee and the participating centers

Members of the scientific advisory committee: Julio Ancochea (Hospital de La Princesa, Madrid), Carlos Badiola (GlaxoSmithKline, Madrid), Enric Duran (IMIM, Barcelona), Francisco García Río (Hospital La Paz, Madrid), Marc Miravitlles (Hospital Clínic i Provincial, Barcelona), Luis Muñoz (Hospital Reina Sofía, Cordoba), Víctor Sobradillo (Hospital de Cruces, Barakaldo, Vizcaya), Joan B. Soriano (Caubet-CIMERA Foundation, Balearic Islands, Mallorca).

Research coordinators at the participating centers: Antoni Torres (Hospital Clínic i Provincial, Barcelona), Francisco García Río (Hospital La Paz, Madrid), Jaime Martínez (Hospital Central de Asturias, Oviedo), Joan Serra (Hospital General de Vic, Vic, Barcelona), José Luis Viejo (Hospital General Yagüe, Burgos), Juan José Soler (Hospital General de Requena, Requena, Valencia), Julio Ancochea (Hospital de La Princesa, Madrid), Luis Borderias (Hospital San Jorge, Huesca), Luis Muñoz (Hospital Reina Sofía, Cordoba), Luis Piñeiro (Hospital Xeral Cies, Vigo, Pontevedra), Teodoro Montemayor (Hospital Virgen Macarena, Seville).

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