Respiratory symptoms and their determinants in the general Spanish population: changes over 20 years

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

[1]Pneumology Dept, Hospital Universitari Vall d'Hebron/Vall d'Hebron Institut de Recerca, Barcelona, Spain. [2]CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain. [3]Servicio de Neumología, Hospital Arnau de Vilanova-Lliria, Valencia, Spain. [4]Servicio de Neumología, Hospital Universitario La Princesa, and Universidad Autónoma de Madrid, Madrid, Spain. [5]Servicio de Neumología, Hospital Universitario La Paz-IdiPAZ, Madrid, Spain. [6]Servicio de Neumología, Hospital General Gregorio Marañon, Madrid, Spain. [7]Unidad de Gestión Clínica de Neumología, Hospital Universitario Virgen de Valme, Universidad de Sevilla, Seville, Spain. [8]Servicio de Neumología, Hospital Universitario Nuestra Señora de Candelaria, Tenerife, Spain. [9]Servicio de Neumología, Hospital Universitario "Príncipe de Asturias", Alcalá de Henares, Universidad de Alcalá, Madrid, Spain. [10]Departamento Médico, GSK, Madrid, Spain. [11]Servicio de Neumología, Hospital Universitario Son Espases-IdISBa, Palma de Mallorca, Spain.

Corresponding author: Marc Miravitlles (marcm@separ.es)

Shareable abstract (@ERSpublications)
Approximately half of the adult Spanish population has some respiratory symptoms and this prevalence has remained quite stable over the last 20 years https://bit.ly/37uGRT7

Cite this article as: Miravitlles M, Soler-Cataluña JJ, Soriano JB, *et al*. Respiratory symptoms and their determinants in the general Spanish population: changes over 20 years. *ERJ Open Res* 2022; 8: 00067-2022 [DOI: 10.1183/23120541.00067-2022].

Received: 3 Feb 2022
Accepted: 1 April 2022

Abstract

Background Few large epidemiological studies have analysed the prevalence of respiratory symptoms and their determinants in the general adult population. We investigated the prevalence and determinants of respiratory symptoms and compared their prevalence with that of two previous studies conducted in 1999 and 2009.

Method EPISCAN II was a multicentre, cross-sectional, population-based epidemiological study in individuals older than 40 years.

Results A total of 9092 individuals were included. Up to 47.5% reported at least one respiratory symptom, being more frequent in women than in men (49.4% *versus* 45.5%, p=0.0002) and with wheezing being the most frequent (33.7%) followed by dyspnoea (26.8%). The presence of any symptom was associated with female sex, higher body mass index (BMI), lower forced expiratory volume in 1 s (FEV_1 % pred), reduced physical activity, a higher Charlson index and the presence of anxiety and depression. Smoking was also significantly associated with having at least one respiratory symptom in a dose–response fashion (OR: 1.415, 1.916, 2.192 and 2.987 for 0–10, 10–20, 20–30 and >30 pack-years, respectively, all p<0.0001). The prevalence of symptoms remained quite similar over the last 20 years (wheezing 40%, 36% and 33.7% and dyspnoea 10.4%, 9.9% and 13.1% in 1999, 2009 and 2019, respectively).

Conclusions Approximately half of the adult Spanish population have respiratory symptoms and this prevalence has remained quite stable over the last 20 years. Smoking remains the main factor associated with respiratory symptoms, but female sex, comorbidities, high BMI and low FEV_1 and low physical activity are also significantly associated with respiratory symptoms.

Introduction

Acute and chronic respiratory symptoms are one of the most frequent causes of consultation to the health system. In fact, cough is the second cause of consultation to primary care physicians [1]. Although some respiratory symptoms may be benign and self-limited, others persist and significantly impair patients' quality of life [2]. Chronic respiratory symptoms in adults may be the manifestation of several respiratory diseases, which are more frequently airways diseases such as asthma, COPD or bronchiectasis. However,

other non-respiratory diseases, particularly, but not exclusively, cardiovascular diseases and anaemia, can also present with chronic respiratory symptoms.

A previous epidemiological study conducted at the end of the last century in Spain in +4000 adults between 40 and 69 years of age showed that 48% reported at least one respiratory symptom, being more frequent in men than in women and with a clear relationship with smoking habits [3]. During the last 20 years significant social changes have occurred in Spain, including more restrictive legislations against smoking, with a reduction in smoking rates in males, but not in females [4]. Moreover, spirometry has become more widely available in primary care, and treatments for asthma and COPD have improved. It is not clear whether these and other aspects may have changed the prevalence of respiratory symptoms and their determinants in the adult population.

The EPISCAN II (in Spanish: Epidemiology of COPD in Spain) is a population-based epidemiological study designed with the main objective of determining the prevalence of COPD in Spain through the analysis of a representative sample of adults from all the Spanish regions (autonomous communities) [5]. This article presents the results of a secondary objective which was to assess the prevalence and determinants of respiratory symptoms in the general adult population. The EPISCAN II study used a similar methodology and the same questionnaires as the IBERPOC study conducted in 1999 [3] and the EPISCAN study conducted in 2009 [6]; therefore, a comparison of the prevalence of respiratory symptoms in these three studies conducted over a period of 20 years was also conducted.

Methods

Study design and population

The EPISCAN II study was a national, multicentre, cross-sectional, population-based epidemiological study aimed at investigating the prevalence of COPD in Spain. The fieldwork was conducted from April 2017 to February 2019 in 20 teaching hospitals from the 17 Spanish autonomous communities. Subjects from the general population who were resident in the postal code areas nearest the participating hospitals were selected. A list of random telephone numbers was obtained, stratified according to these postal codes and quotas for sex and age groups. The inclusion criteria were as follows: men or women aged 40 years or more with no physical or cognitive difficulties that would prevent them from completing spirometry or any of the study procedures. The protocol, the fieldwork and all the methods have been described previously [5, 7]. In this article we present the results of one of the secondary outcomes, the prevalence and determinants of respiratory symptoms in the general Spanish adult population.

The study was approved by the ethics committees of each of the participating centres, 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.

Variables and procedures

Demographic information on sex, age, level of education, comorbidities, weight, height and smoking were collected. A smoker was defined as an individual who smoked at least one cigarette, cigar or pipe a day, and an ex-smoker was defined as an individual who had discontinued using any form of tobacco at least 6 months before the study visit. Comorbidities were assessed with the Charlson index [8]. Forced spirometry pre- and post-bronchodilation was performed using a pneumotachograph (Vyntus Spiro, Carefusion, Germany), according to standardised procedures as previously described [5, 9].

For the diagnosis of respiratory symptoms, the answers to the European Community for Coal and Steel Questionnaire (ECSC) were used [10]. The diagnosis of cough was considered when the participant answered yes to any of the following questions: Do you usually cough when you get up? Do you usually cough during the day or during the night? Chronic expectoration was considered when there was an affirmative answer to: Do you usually cough up phlegm during the day or during the night? Dyspnoea was diagnosed when a positive answer was given to: Do you get breathless when going up one flight of stairs at your normal pace? Wheezing was evaluated by the question: Have you ever had wheezing or whistling in your chest? Chronic bronchitis was diagnosed when the answer was yes to the question: Do you cough up phlegm most days or nights for 3 months each year? A diagnosis of asthma was accepted when the participant answered yes to: Has a doctor ever told you that you have asthma? The degree of dyspnoea was evaluated by the modified Medical Research Council (mMRC) dyspnoea scale, that ranges between 0 – I only get breathless with strenuous exercise – to 4 – I am too breathless to leave the house, or I get breathless when dressing [11].

Health status was assessed by the COPD Assessment Test (CAT) questionnaire. The CAT is a disease-specific questionnaire consisting of eight items: cough, expectoration, chest tightness, difficulty going up hills/stairs, confidence leaving home, activity limitations at home, quality of sleep and levels of energy, each presented as a 5-point scale, providing a total score of 0 (floor) to 40 (ceiling) indicating the impact of the disease [12].

Depression was identified through a clinical interview using the Hospital Anxiety and Depression Scale (HADS), which is a tool validated for use in Spanish and used for the assessment of symptoms and the identification of cases of anxiety and depression in patients with chronic disease [13]. This questionnaire includes seven items of depression (depression subscale or HADS-D) and seven of anxiety (anxiety subscale or HADS-A). In each subscale the scores range from 0 to 21. Possible depression or anxiety was classified in patients scoring >8 in the respective HADS subscales.

Physical activity was measured by the Yale Physical Activity Questionnaire (YPAS) validated for the Spanish population and the elderly population. This questionnaire reflects the amount, frequency and intensity of physical activity that can be used to estimate the effects of physical activity as a continuous parameter, even at the low levels of activity that might be expected in COPD patients [14, 15].

Statistical analysis

Categorical variables were presented as numbers with percentages, and continuous variables as mean±SD. The characteristics of the population and the prevalence of symptoms according to sex and smoking status were compared using the t-test, or χ^2 test. The prevalence of symptoms among the different surveys was compared with the χ^2 test for trend. Univariate and multivariate linear regression analyses were used to investigate factors associated with respiratory symptoms. Only variables with a level of significance <0.1 in the univariate analysis were included in a stepwise multivariate linear regression model. The R2 coefficient of determination was calculated for the model. Data were analysed with the Statistical Analysis System (SAS) Enterprise Guide 7.15, considering a statistical significance (p) of 0.05 for all the statistical tests performed.

Results

Population characteristics

Overall, a total of 12 825 subjects were initially contacted by phone, and 9092 (70.9%) agreed to be seen in the hospital and performed a valid spirometry and constituted the population of our study. The characteristics of the population are described in table 1.

TABLE 1 Demographic and clinical characteristics of the study participants by sex and smoking

	Global	Men	Women	p-value	Smokers	Never-smokers	p-value
Subjects n	9092	4311	4781		4910	4182	
Age years	60.2±11.1	60.1±10.8	60.4±11.3	0.1553	59.4±10.2	61.2±12.0	<0.0001
BMI kg·m^{-2}	27.5±5.0	28.1±4.4	27.01±5.4	<0.0001	27.4±4.8	27.6±5.1	0.0706
Active smoker %	19.8	21.6	18.1	<0.0001	36.6		
Ex-smoker %	34.2	39.9	29.1		63.4		
Never-smoker %	46.0	38.5	52.8			100	
Pack-years	26.3±22.9	30.0±24.8	21.9±19.6	<0.0001	26.3±22.9		
FVC L	3.7±1.0	4.32±0.9	3.1±0.7	<0.0001	3.8±0.9	3.2±1.1	<0.0001
FVC %	101.0±14.9	100.5±14.9	101.5±14.9	<0.0001	100.9±14.5	101.2±15.4	0.2152
FEV_1 L	2.9±0.8	3.34±0.8	2.4±0.6	<0.0001	2.9±0.8	2.8±0.9	<0.0001
FEV_1 % pred	100.6±17.1	99.64±17.7	101.5±16.5	<0.0001	98.8±17.2	102.7±16.8	<0.0001
FEV_1/FVC	78.2±7.8	77.08±8.5	79.12±7.04	<0.0001	76.9±8.5	79.7±6.7	<0.0001
Charlson comorbidity index	0.36±0.87	0.42±0.97	0.30±0.77	<0.0001	0.40±0.94	0.30±0.78	<0.0001
COTE index	1.01±2.25	0.64±1.72	1.34±2.59	<0.0001	1.06±2.29	0.95±2.20	0.0256
Possible depression %	11.1	9.5	12.6	<0.0001	11.0	11.2	0.9141
Possible anxiety %	26.6	19.7	32.8	<0.0001	26.4	26.8	0.1447
YPAS	50.0±23.8	52.7±25.1	47.7±22.5	<0.0001	50.0±23.9	50.1±14.0	0.8135

Values are mean±SD, unless otherwise specified. BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; COTE: COPD specific comorbidity test; YPAS: Yale Physical Activity Questionnaire.

Prevalence of respiratory symptoms

Up to 47.5% of the population reported at least one respiratory symptom, being more frequent in women than men (49.4% *versus* 45.5%, p=0.0002), and the most frequent was wheezing (33.7%) followed by any dyspnoea (26.8%) and cough (15.9%). The different respiratory symptoms were significantly more frequent in women except for wheezing and chronic bronchitis (table 2, figure 1a). However, the prevalence of airflow limitation by both fixed ratio and lower limit of normal (LLN) was significantly more frequent in men (table 2). The mean±SD CAT score was 6.4±5.8, being higher in women than men (6.8±6.1 *versus* 5.8±5.4; p<0.0001), and up to 22.8% of women had a CAT >10 compared with 16.2% of men (p<0.0001).

Up to 55.4% of smokers had at least one respiratory symptom compared with 38.3% of never-smokers (p<0.0001). All individual respiratory symptoms were significantly more frequent in smokers compared to never-smokers, except for dyspnoea evaluated either as dyspnoea at one floor, as any dyspnoea or as the mMRC degree of dyspnoea (table 2, figure 1b). The prevalence of airflow limitation by both definitions, the CAT scores and the proportion of subjects with CAT >10 were also higher in smokers compared with never-smokers (table 2). However, the presence of asthma was significantly lower in smokers compared with never-smokers (6.6% *versus* 9.4%; p<0.0001).

Prevalence of comorbidities and level of physical activity

The population included had a low prevalence of comorbidities, with a mean±SD Charlson score of 0.36±0.87, which was significantly higher in men than in women and in smokers than in never-smokers. Up to 11.1% of participants had a HAD score consistent with possible depression and 26.6% of possible anxiety, both of which were higher in women than in men, but without differences between smokers and never-smokers.

The mean±SD YPAS score was 50±23.8, being higher in men, but with no differences between smokers and never-smokers (table 1).

Factors associated with respiratory symptoms

In the multivariate analysis, dyspnoea was significantly and strongly associated with female sex (odds ratio (OR) 3.056, 95% CI 2.597–3.597; p<0.0001) and comorbidities, and especially with anxiety and depression. There was also an association with increasing age and the body mass index (BMI) and with a smoking consumption of >30 pack-years and a significant negative association with forced expiratory volume in 1 s (FEV_1 % pred) and the YPAS score (table 3).

TABLE 2 Prevalence of respiratory symptoms and chronic airflow obstruction in the study participants by sex and smoking

	Global	Men	Women	p-value	Smokers	Never-smokers	p-value
Subjects n	9092	4311	4781		4910	4182	
Chronic cough	15.9	14.9	16.8	0.0146	19.5	11.6	<0.0001
CMH	13.0	15.0	11.2	<0.0001	17.0	8.3	<0.0001
Wheezing	33.7	33.6	33.8	0.7927	41.4	24.7	<0.0001
Dyspnoea one floor	13.1	8.3	17.5	<0.0001	13.4	12.8	0.4333
Any dyspnoea	26.8	22.0	31.1	<0.0001	27.0	26.5	0.6041
Dyspnoea mMRC				<0.0001			0.9011
0	73.2	78.0	68.9		73.0	73.5	
I	21.8	18.1	25.1		21.9	21.6	
II	3.8	2.9	4.7		3.8	3.9	
III	1.1	1.0	1.2		1.2	1.0	
IV	0.1	0.1	0.1		0.1	0.1	
Chronic bronchitis	4.7	5.0	4.3	0.1387	6.7	2.3	<0.0001
Any symptom	47.5	45.5	49.4	0.0002	55.4	38.3	<0.0001
CAT score, mean±SD	6.4±5.8	5.8±5.4	6.8±6.1	<0.0001	6.8±5.8	5.9±5.7	<0.0001
CAT >10	19.6	16.2	22.8	<0.0001	21.5	17.5	<0.0001
Asthma	7.9	6.2	9.4	<0.0001	6.6	9.4	<0.0001
Chronic airflow limitation (FR)	11.8	14.6	9.4	<0.0001	16.0	7.0	<0.0001
Chronic airflow limitation (LLN)	6.0	7.1	4.9	<0.0001	8.8	2.7	<0.0001

Values are % unless otherwise specified. CMH: chronic mucus hypersecretion; mMRC: Modified Medical Research Council dyspnoea scale; CAT: COPD Assessment Test; FR: fixed ratio; LLN: lower limit of normal.

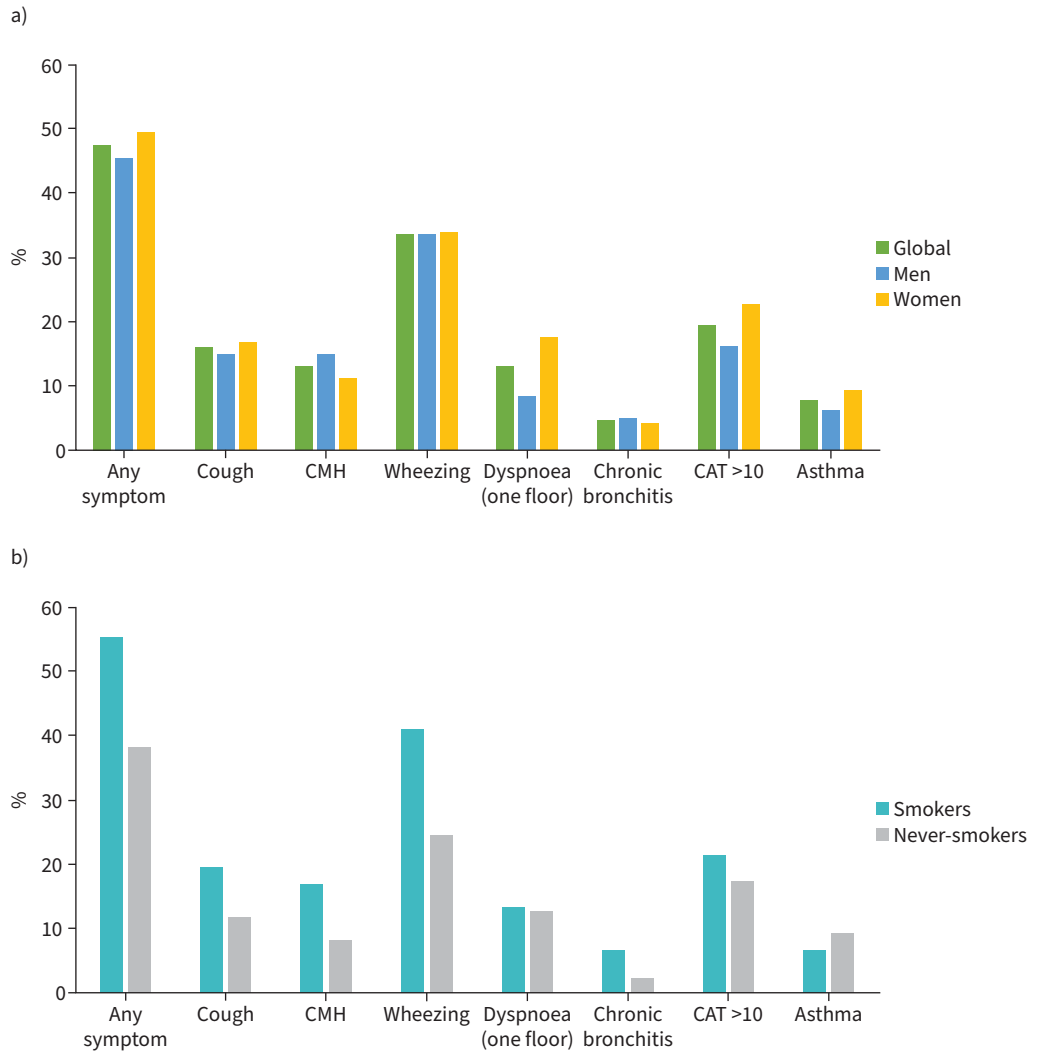

FIGURE 1 Prevalence of respiratory symptoms in the general population over 40 years of age by a) sex and b) smoking habit. CMH: chronic mucus hypersecretion; CAT: COPD Assessment Test.

Wheezing was significantly associated with smoking, with increasing odds ratios at different levels of consumption (OR 1.627, 1.930, 2.138 and 2.659 at 0–10, 10–20, 20–30 and >30 pack-years, respectively, all p>0.0001). It was also associated with increasing BMI and increasing comorbidities, including anxiety but not depression (table 3).

Regarding chronic bronchitis, there was an association with increasing smoking consumption starting at 10–20 pack-years with OR 1.803 (95% CI 1.223–2.657; p=0.0029), which increased to OR 3.069 and 4.808 for 20–30 and >30 pack-years, respectively (both p<0.0001). It was also significantly associated with depression (OR 1.388, 95% CI 1.040–1.852; p=0.0259) and anxiety (OR 2.457; 95% CI 1.940–3.110; p<0.0001) and negatively associated with FEV_1 % pred (table 4).

The presence of any symptom was associated with female sex (OR 1.435; 95% CI 1.302–1.582; p<0.0001), a higher BMI, having at least a Charlson score of 1 compared to 0, and the presence of anxiety and depression. Smoking was also significantly associated with having at least one respiratory symptom in a dose–response fashion with increasing odds ratios for increasing smoking consumption (OR 1.415, 1.916, 2.192 and 2.987 for 0–10, 10–20, 20–30 and >30 pack-years, respectively, all p<0.0001). Having any respiratory symptom was negatively associated with FEV_1 % pred and physical activity measured by the YPAS (table 4).

TABLE 3 Unadjusted and adjusted association between patients' characteristics and the presence of dyspnoea and wheezing

Variables	Dyspnoea				Wheezing			
	Unadjusted analysis		Adjusted analysis		Unadjusted analysis		Adjusted analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex								
Male	Ref		Ref		Ref			
Female	2.355 (2.062–2.691)	<0.0001	3.056 2.597–3.597)	<0.0001	1.012 (0.927–1.105)	0.7928		
Age years	1.039 (1.033–1.045)	<0.0001	1.029 (1.022–1.036)	<0.0001	0.997 (0.993–1.001)	0.2092		
BMI kg·m^{-2}	1.111 (1.098–1.124)	<0.0001	1.093 (1.078–1.107)	<0.0001	1.054 (1.045–1.064)	<0.0001	1.043 (1.033–1.052)	<0.0001
Smoking pack-years								
0	Ref		Ref		Ref		Ref	
0–10	0.775 (0.632–0.951)	0.0145	1.162 (0.919–1.470)	0.2107	1.448 (1.263–1.661)	<0.0001	1.627 (1.409–1.879)	<0.0001
10–20	0.748 (0.598–0.935)	0.0107	1.076 (0.835–1.386)	0.5704	1.818 (1.575–2.099)	<0.0001	1.930 (1.659–2.245)	<0.0001
20–30	0.930 (0.748–1.158)	0.5175	1.252 (0.972–1.612)	0.0815	2.154 (1.857–2.499)	<0.0001	2.138 (1.828–2.502)	<0.0001
>30	1.593 (1.362–1.864)	<0.0001	1.529 (1.262–1.854)	<0.0001	3.242 (2.870–3.662)	<0.0001	2.659 (2.334–3.029)	<0.0001
FEV_1 %	0.966 (0.963–0.970)	<0.0001	0.973 (0.969–0.977)	<0.0001	0.972 (0.970–0.975)	<0.0001	0.978 (0.975–0.981)	<0.0001
Charlson comorbidity index								
0	Ref		Ref		Ref			
1	2.503 (2.147–2.919)	<0.0001	1.700 (1.420–2.036)	<0.0001	1.780 (1.578–2.009)	<0.0001	1.372 (1.203–1.566)	<0.0001
>1	3.409 (2.826–4.112)	<0.0001	2.341 (1.873–2.926)	<0.0001	1.665 (1.417–1.957)	<0.0001	1.211 (1.015–1.446)	0.0335
Depression	4.167 (3.582–4.847)	<0.0001	1.945 (1.606–2.356)	<0.0001	1.543 (1.349–1.765)	<0.0001		
Anxiety	3.050 (2.685–3.464)	<0.0001	2.302 (1.956–2.709)	<0.0001	1.762 (1.599–1.942)	<0.0001	1.769 (1.595–1.963)	<0.0001
YPAS	0.975 (0.972–0.978)	<0.0001	0.986 (0.983–0.989)	<0.0001	0.995 (0.993–0.997)	<0.0001		

The analysis was adjusted for the following variables: body mass index (BMI); forced vital capacity (FVC); forced expiratory volume in 1 s (FEV_1); Hospital Anxiety and Depression scale (HADS); Yale Physical Activity Questionnaire (YPAS). Ref: reference.

The adjusted and unadjusted analyses separately by men and women are presented in the supplementary material (tables S1 to S4). In general, the association between respiratory symptoms and cumulative smoking consumption was stronger in men and that of depression and anxiety and symptoms was stronger in women. Age was only significantly associated with the presence of any symptom in women but not in men.

Changes in the prevalence of respiratory symptoms over 20 years

The prevalence of respiratory symptoms in the IBERPOC, EPISCAN and EPISCAN II studies was compared. The main characteristics of the population included in the three studies are presented in the supplementary material (table S5). The distribution of the populations by sex and smoking habits was very similar, but the mean age increased progressively from IBERPOC to EPISCAN and EPISCAN II due to the modified inclusion criteria. Nevertheless, the prevalence of symptoms was very similar among the surveys, with a slight but significant increase in dyspnoea, cough, sputum production and diagnosis of asthma and a decrease in wheezing, while the prevalence of chronic airflow obstruction ranged between 10.2% in EPISCAN and 11.8% in EPISCAN II and with an intermediate value in IBERPOC (10.6%) (figure 2 and supplementary table S5). Supplementary table S6 shows the comparison between IBERPOC and EPISCAN and the participants of the same age group in EPISCAN II. Prevalence of symptoms was very similar, with some differences reaching statistical significance due to the large sample size.

Discussion

The EPISCAN II study which included >9000 adult participants is the largest epidemiological study on COPD and respiratory symptoms conducted in Spain [5]. It has provided an accurate estimate of the prevalence of COPD [7] and has also collected important information about the prevalence of respiratory symptoms and their determinants in a representative sample of the global Spanish population. The results show that almost half of the Spanish adult population reports at least one respiratory symptom, wheezing being the most prevalent, followed by dyspnoea. The majority of symptoms were more frequent in women, and women also had worse CAT scores despite having a higher proportion of never-smokers than men. However, the prevalence of chronic bronchitis and airflow limitation was higher in men. All respiratory symptoms, except dyspnoea, were more frequent in smokers than in never-smokers; conversely, the prevalence of asthma was higher in never-smokers. We have also shown that this burden of symptoms on the Spanish population has changed little over the last 20 years.

TABLE 4 Unadjusted and adjusted association between patients' characteristics and chronic bronchitis and the presence of "any symptom"

Variables	Chronic bronchitis				"Any symptom"			
	Unadjusted analysis		Adjusted analysis		Unadjusted analysis		Adjusted analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex								
Male	Ref				Ref		Ref	
Female	0.859 (0.703–1.051)	0.1391			1.171 (1.076–1.274)	0.0002	1.435 (1.302–1.582)	<0.0001
Age years	1.006 (0.997–1.015)	0.1891			1.010 (1.006–1.014)	<0.0001		
BMI kg·m^{-2}	1.029 (1.010–1.049)	0.0025			1.063 (1.054–1.073)	<0.0001	1.051 (1.041–1.062)	<0.0001
Smoking pack-years								
0	Ref		Ref		Ref		Ref	
0–10	1.174 (0.784–1.757)	0.4360	1.258 (0.828–1.911)	0.2829	1.221 (1.073–1.389)	0.0025	1.415 (1.232–1.625)	<0.0001
10–20	1.769 (1.222–2.582)	0.0031	1.803 (1.223–2.657)	0.0029	1.703 (1.484–1.955)	<0.0001	1.916 (1.651–2.224)	<0.0001
20–30	3.097 (2.216–4.327)	<0.0001	3.069 (2.174–4.333)	<0.0001	2.038 (1.762–2.356)	<0.0001	2.192 (1.872–2.566)	<0.0001
>30	5.726 (4.409–7.435)	<0.0001	4.808 (3.655–6.324)	<0.0001	3.377 (2.982–3.824)	<0.0001	2.987 (2.605–3.426)	<0.0001
FEV_1 %	0.968 (0.963–0.973)	<0.0001	0.977 (0.971–0.982)	<0.0001	0.969 (0.966–0.971)	<0.0001	0.975 (0.972–0.978)	<0.0001
Charlson comorbidity index								
0	Ref				Ref		Ref	
1	1.629 (1.257–3.113)	0.0002			1.909 (1.690–2.156)	<0.0001	1.457 (1.273–1.667)	<0.0001
>1	2.184 (1.607–2.968)	<0.0001			2.119 (1.797–2.498)	<0.0001	1.537 (1.280–1.845)	<0.0001
Depression	2.774 (2.177–3.535)	<0.0001	1.388 (1.040–1.852)	0.0259	2.210 (1.923–2.541)	<0.0001	1.240 (1.050–1.464)	0.0113
Anxiety	2.723 (2.222–3.337)	<0.0001	2.457 (1.940–3.110)	<0.0001	2.029 (1.841–2.236)	<0.0001	1.825 (1.626–2.048)	<0.0001
YPAS	0.992 (0.987–0.996)	0.0003			0.991 (0.989–0.993)	<0.0001	0.996 (0.994–0.998)	<0.0001

The analysis was adjusted for the following variables: body mass index (BMI); forced vital capacity (FVC); forced expiratory volume in 1 s (FEV_1); Hospital Anxiety and Depression scale (HADS); Yale Physical Activity Questionnaire (YPAS). Ref: reference.

Several studies have described the prevalence and characteristics of respiratory symptoms in patients with respiratory diseases, or in relation to environmental or professional activities, but only a few epidemiological surveys have provided estimates of the prevalence of respiratory symptoms and their determinants in the general adult population. Comparisons of prevalence of respiratory symptoms between studies must be made with caution, because of differences in age composition and smoking habits of the populations included, and especially due to the use of different symptoms questionnaires. Nevertheless, all

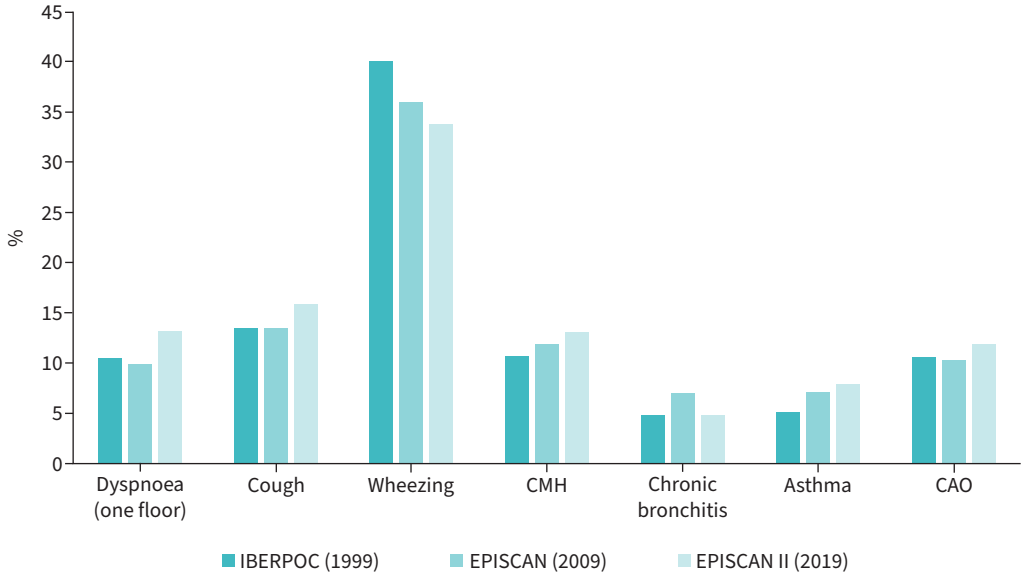

FIGURE 2 Prevalence of respiratory symptoms in three population-based epidemiological surveys conducted in Spain in 1999, 2009 and 2019. CMH: chronic mucus hypersecretion; CAO: chronic airflow obstruction.

surveys agree on the high prevalence of respiratory symptoms in the general population. In a random sample of adults between 20 and 69 years in Nordic European countries, between 54% and 66% of participants in the participating countries presented at least one respiratory symptom [16], similar to the 50% observed among almost 20 000 subjects from Norway [17], the 49.7% of 786 subjects without COPD interviewed in Sweden [18], and also very close to the 47.5% obtained in our study. This high prevalence is very relevant because the presence of respiratory symptoms, even in subjects with normal lung function, has been associated with a significant impairment in quality of life [2]. Furthermore, our data have shown a significant association between respiratory symptoms in general and dyspnoea in particular, with a higher prevalence of depression and anxiety and reduced levels of physical activity. These results suggest that these factors may interact and constitute a vicious circle that requires a precise diagnosis and a multidisciplinary approach.

The presence of respiratory symptoms also has important prognostic implications. Some prospective studies have demonstrated that adults with respiratory symptoms have an increased risk of being diagnosed in the future with a lung disease and an accelerated decline in lung function [19], more respiratory hospitalisations and even an increased risk of death [20, 21]. Nonetheless, the importance of respiratory symptoms may not be perceived by the individuals suffering from them. A large survey conducted in 2005 in +6500 subjects in Spain indicated that only 60% of respondents with respiratory symptoms had consulted a physician and, of these, only 45% had undergone spirometry [22]. 15 years later, the proportion of symptomatic subjects who consulted a physician remained at 59.3%, but the use of spirometry among these subjects improved to up to 66.2% [23].

Wheezing was the most prevalent symptom in our population (33.7%), followed by dyspnoea (26.8%). Similarly, Abrahamsen *et al.* [24] found a prevalence of wheezing of 27% in a study in 16 000+ individuals between 16 and 50 years of age, and a prevalence of 23.4% of wheezing was observed among ever-smoking women between 40 and 69 years in a Korean population [25]. The prevalence of dyspnoea is more variable among surveys probably due to the different definitions and scales used. In the aforementioned Korean study, the prevalence of dyspnoea ranged from 23.8% in non-smoking men to 58.6% in smoking women [25]. In a study on 1500 individuals with a mean age of 49 years, Vinnikov *et al.* [26] found a prevalence of dyspnoea mMRC >2 of 9%, which was higher than the 5% in our study. In a survey of 1000+ individuals older than 40 years in Brazil, the prevalence of dyspnoea ranged from 19% in subjects with normal weight to 36% in obese individuals [27]. The significant association of increased BMI with dyspnoea was also observed in our population, together with a higher prevalence of dyspnoea in women, despite a lower percentage of ever-smokers among women.

All respiratory symptoms were significantly associated in a dose–response fashion with smoking. The impact of smoking on symptoms and respiratory health in general are well documented [18, 24, 25, 28], but other factors such as comorbidities may also be significantly associated with respiratory symptoms. In addition to a higher BMI, a higher Charlson comorbidity index and greater anxiety and depression were associated with wheezing and dyspnoea in our study. Conversely, chronic bronchitis was not significantly associated with BMI and the Charlson index indicating the clear respiratory origin of this symptom.

The CAT questionnaire has been extensively used to evaluate symptoms in patients with COPD, and a CAT score >10 has been considered as a high level of symptoms [29, 30]. The mean CAT score in our population was 6.4, being higher in women than men (6.8 *versus* 5.8), but almost 20%, including 17.5% of never-smokers, presented a CAT score >10. There are few data about CAT scores in large samples of the general adult population, but our results are consistent with a study in 1500 adults in Kazakhstan in which 15% of the participants had a CAT score >10 [26]. Although CAT is considered a symptoms' questionnaire and is used to modulate COPD pharmacologic treatment [30, 31], up to 38% of the variance in CAT scores may be due to non-respiratory factors such as depression [32], which may explain why up to one fifth of the adult population in our study had CAT scores >10. In fact, up to 54% of the individuals in our study with a CAT score >10 had some degree of depression.

The EPISCAN II study is the third of a series of respiratory epidemiological surveys conducted in the general Spanish adult population over the course of 20 years. The three studies used a similar methodology and, in particular, they all used the European Community for Coal and Steel Questionnaire (ECSC) to investigate the prevalence of respiratory symptoms [3, 5, 22]. In a previous comparative study, Soriano *et al.* [33] reported a slight reduction in the prevalence of COPD between the first two studies. In the current analysis, we observed that despite some differences in the characteristics of the populations included in the three studies, the prevalence of respiratory symptoms has remained quite stable over the course of 20 years. Only wheezing decreased slightly, while dyspnoea, cough, chronic mucus

hypersecretion and asthma increased. The small increase in some of the respiratory symptoms may be explained at least in part by the older age of the population of EPISCAN II, which was 60.2 years compared with 56.6 years in EPISCAN [22] and 53.4 years in IBERPOC [3]. In fact, when comparisons were made between the prevalence of symptoms in the previous surveys and the corresponding age groups of EPISCAN II, the prevalence of symptoms were even more similar, with only small increases in cough and mucus hypersecretion in relation to IBERPOC and in cough and dyspnoea in relation to EPISCAN. A moderate increase in respiratory symptoms has also recently been reported in Sweden in a study that compared two different populations of individuals aged 16–75 years 8 years apart [34].

The main limitation of our study is derived from its cross-sectional design that does not allow establishing cause–effect relationships. It is very likely that increased depression and anxiety and reduced physical activity are a consequence of the presence of respiratory symptoms, but we cannot rule out the fact that anxiety and depression can make the subjects more sensitive to the sensation of shortness of breath, or that inactivity may generate deconditioning and therefore shortness of breath with activities of the daily life [35]. Other limitations derive from the definitions of symptoms used in the current study. We used the same questionnaire and same definitions as those in the previous surveys, but it has been demonstrated that some variability may exist, not only due to different diagnostic tools, but also due to language and geographical location [36, 37].

Conclusions

Approximately half of the adult Spanish population has some respiratory symptoms, and the prevalence of respiratory symptoms has remained stable or slightly increased over the last 20 years. Smoking remains the main factor associated with respiratory symptoms, but chronic diseases, a high BMI, low FEV_1 % pred and reduced physical activity are also significantly associated with respiratory symptoms. Female sex was strongly associated with a higher prevalence of dyspnoea.

Provenance: Submitted article, peer reviewed.

Acknowledgements: The collaboration of Monica Sarmiento and Neus Canal of IQVIA, and Carolina Peña and José Julio Jiménez from GSK is explicitly acknowledged.

The following investigators have participated in EPISCAN II. Scientific Committee: Inmaculada Alfageme, Pilar de Lucas, Julio Ancochea, Marc Miravitlles, Juan José Soler-Cataluña, Francisco García-Río, Ciro Casanova, José Miguel Rodríguez González-Moro, Borja G. Cosio, Guadalupe Sánchez, and Joan B Soriano. Principal investigators (PIs), collaborators and participating centres: Madrid: H. La Princesa: Julio Ancochea Bermudez (PI), Elena García Castillo, Claudia Valenzuela and Joan B. Soriano. Castilla León: H.U. de Burgos: Ana Pueyo Bastida (PI), Lourdes Lázaro Asegurado, Luis Rodríguez Pascual and Maria José Mora. Aragón: H. Gral. San Jorge: Luis Borderias Clau (PI), Lourdes Arizón Mendoza and Sandra García. Extremadura: H. San Pedro de Alcántara: Juan Antonio Riesco Miranda (PI), Julián Grande Gutiérrez, Jesús Agustín Manzano and Manuel Agustín Sojo González. Castilla León: H. Clínico U. de Salamanca: Miguel Barrueco Ferrero (PI) and Milagros Rosales. Galicia: H. Álvaro Cunqueiro: José Alberto Fernández Villar (PI), Cristina Represas, Ana Priegue, Isabel Portela Ferreño, Cecilia Mouronte Roibás and Sara Fernández García. I. Baleares: H. Son Espases: Borja G. Cosío (PI), Rocío Cordova Díaz, Nuria Toledo Pons and Margalida Llabrés. Aragón: HU Miguel Servet: José María Marín Trigo (PI), Marta Forner, Begoña Gallego, Pablo Cubero and Elisabet Vera. C. Valenciana: H. Arnau de Vilanova, Valencia: Juan José Soler Cataluña (PI), Maria Begoña Picurelli Albero and Noelia González García. Andalucía: H. Virgen de la Macarena: Agustín Valido Morales (PI), Carolina Panadero, Cristina Benito Bernáldez, Laura Martín-Bejarano and Maria Velarde. Murcia: H. Gral. U. Santa Lucía, Cartagena: Antonio Santa Cruz Siminiani (PI), Carlos Castillo Quintanilla, Rocío Ibáñez Meléndez, José Javier Martínez Garcerán, Desirée Lozano Vicente, Pedro García Torres and Maria del Mar Valdivia. Navarra: Clínica Universidad de Navarra: Juan Pablo de Torres Tajes (PI), Montserrat Cizur Girones and Carmen Labiano Turrillas. La Rioja: H. de San Pedro, Logroño: Carlos Ruiz Martínez (PI), Elena Hernando, Elvira Alfaro, José Manuel García and Jorge Lázaro. País Vasco: H. Santiago Apóstol (H. Txagorritxu): David Bravo (PI), Laura Hidalgo, Silvia Francisco Terreros, Iñaki Zorrilla and Ainara Alonso Colmenero. Asturias: H. Central de Asturias: Cristina Martínez González (PI), Susana Margon, Rosirys Guzman Taveras, Ramón Fernández and Alicia Álvarez. Cantabria: H. de Valdecilla (Servicio de Neumología en el H. Santa Cruz de Liencres): José Ramón Agüero Balbín (PI) and Juan Agüero Calvo. Cataluña: HU Vall d'Hebron: Jaume Ferrer Sancho (PI), Esther Rodríguez González and Eduardo Loeb. Castilla la Mancha: HU de Guadalajara: José Luis Izquierdo Alonso (PI) and Maria Antonia Rodríguez García. I. Canarias: H.U. de Tenerife: Juan Abreu González (PI), Candelaria Martín García, Rebeca Muñoz and Haydée Martín García. Asturias: H.U. de San Agustín, Avilés: Miguel Angel Martínez Muñiz (PI), 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 and Juan Diego Alvarez Mavárez.

Availability of data and materials: Information on the GSK data sharing commitments and requesting access to anonymised individual participant data and associated documents can be found at www.clinicalstudydatarequest.com.

Author contributions: The study concept and design: M. Miravitlles, J.J. Soler-Cataluña, J.B. Soriano, F. García-Río, P. de Lucas, I. Alfageme, C. Casanova, J.M.R. González-Moro, G. Sánchez, J. Ancochea and B.G. Cosío. Data acquisition: J.J. Soler-Cataluña, J. Ancochea and B.G. Cosío. Analysis and interpretation of the data: M. Miravitlles, J.J. Soler-Cataluña, J.B. Soriano and B.G. Cosío. Drafting of the manuscript: M. Miravitlles. Critical revision and approval for submission: M. Miravitlles, J.J. Soler-Cataluña, J.B. Soriano, F. García-Río, P. de Lucas, I. Alfageme, C. Casanova, J.M.R. González-Moro, G. Sánchez, J. Ancochea and B.G. Cosío. All authors have read and approved the final manuscript.

Conflict of interest: M. 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. J.J. Soler-Cataluña has received speaker fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Esteve, Ferrer, GlaxoSmithKline, Menarini, Novartis and Teva, and consulting fees from AstraZeneca, Bial, Boehringer Ingelheim, GlaxoSmithKline, Ferrer and Novartis. F. 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. J. 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 and Teva. C. Casanova has received speaker or consulting fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini and Novartis, and research grants from GlaxoSmithKline, Menarini and AstraZeneca. J.M.R. González-Moro has recieved research grants from GSK and Grifols, outside the submitted work; and speaker or consulting fees from AstraZeneca, Chiesi, GlaxoSmithKline, Meiji, and Orion pharma, outside the submitted work. G. Sanchez is a GlaxoSmithKline employee within the Medical Dept. B.G. Cosio has received speaker or consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Novartis, Sanofi and TEVA, and research grants from Menarini, AstraZeneca and Boehringer Ingelheim. J.B. Soriano, P. de Lucas and I. Alfageme have no conflicts of interest.

Support statement: The EPISCAN II study was sponsored by GlaxoSmithKline. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Zervanos NJ, Shute KM. Acute, disruptive cough. Symptomatic therapy for a nagging problem. *Postgrad Med* 1994; 95: 153–164.
2 Voll-Aanerud M, Eagan TM, Plana E, *et al.* Respiratory symptoms in adults are related to impaired quality of life, regardless of asthma and COPD: results from the European community respiratory health survey. *Health Qual Life Outcomes* 2010; 8: 107.
3 Sobradillo V, Miravitlles M, Jiménez CA, *et al.* Epidemiological study of chronic obstructive pulmonary disease in Spain (IBERPOC): prevalence of chronic respiratory symptoms and airflow limitation. *Arch Bronconeumol* 1999; 35: 159–166.
4 Martín Álvarez JM, Almeida A, Golpe AA, *et al.* [The influence of cigarette price on the cigarette consumption in Spain: a Logarithmic Mean Divisia Index analysis from 1957 to 2018]. *Rev Esp Salud Publica* 2021; 95: e202102026.
5 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; 55: 38–47.
6 Miravitlles M, Soriano JB, García-Río F, *et al.* Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax* 2009; 64: 863–868.
7 Soriano JB, Alfageme I, Miravitlles M, *et al.* Prevalence and determinants of COPD in Spain: EPISCAN II. *Arch Bronconeumol (Engl Ed)* 2021; 57: 61–69.
8 Charlson ME, Szatrowski TP, Peterson J, *et al.* Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; 47: 1245–1251.
9 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
10 Minette A. Questionnaire of the European Community for Coal and Steel (ECSC) on respiratory symptoms. 1987 – updating of the 1962 and 1967 questionnaires for studying chronic bronchitis and emphysema. *Eur Respir J* 1989; 2: 165–177.
11 Bestall C, Paul EA, Garrod R, *et al.* Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; 54: 581–586.

12 Jones PW, Harding G, Berry P, *et al.* Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009; 34: 648–654.
13 Herrero MJ, Blanch J, Peri JM, *et al.* A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. *Gen Hosp Psychiatry* 2003; 25: 277–283.
14 De Abajo S, Larriba R, Márquez S. Validity and reliability of the Yale Physical Activity Survey in Spanish elderly. *J Sports Med Phys Fitness* 2001; 41: 479–485.
15 Donaire-González D, Gimeno-Santos E, Serra I, *et al.* Validation of the Yale Physical Activity Survey in chronic obstructive pulmonary disease patients. *Arch Bronconeumol* 2011; 47: 552–560.
16 Axelsson M, Lindberg A, Kainu A, *et al.* Respiratory symptoms increase health care consumption and affect everyday life - a cross-sectional population-based study from Finland, Estonia, and Sweden. *Eur Clin Respir J* 2016; 3: 31024.
17 Frostad A, Søyseth V, Andersen A, *et al.* Respiratory symptoms as predictors of all-cause mortality in an urban community: a 30-year follow-up. *J Intern Med* 2006; 259: 520–529.
18 Stridsman C, Müllerova H, Skär L, *et al.* Fatigue in COPD and the impact of respiratory symptoms and heart disease: a population-based study. *COPD* 2013; 10: 125–132.
19 Kalhan R, Dransfield MT, Colangelo LA, *et al.* Respiratory symptoms in young adults and future lung disease. The CARDIA Lung Study. *Am J Respir Crit Care Med* 2018; 197: 1616–1624.
20 Çolak Y, Nordestgaard BG, Vestbo J, *et al.* Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry. *Eur Respir J* 2019; 54: 1900734.
21 Gulsvik A, Bakke PS, Brøgger J, *et al.* Respiratory symptoms and mortality in four general population cohorts over 45 years. *Respir Med* 2020; 170: 106060.
22 Miravitlles M, de la Roza C, Morera J, *et al.* Chronic respiratory symptoms, spirometry and knowledge of COPD among general population. *Respir Med* 2006; 100: 1973–1980.
23 Calle Rubio M, Rodríguez Hermosa JL, Miravitlles M, *et al.* Knowledge of chronic obstructive pulmonary disease, presence of chronic respiratory symptoms and use of spirometry among the Spanish population: CONOCEPOC 2019 study. *Arch Bronconeumol* 2021; 57: 741–749.
24 Abrahamsen R, Fell AK, Svendsen MV, *et al.* Association of respiratory symptoms and asthma with occupational exposures: findings from a population-based cross-sectional survey in Telemark, Norway. *BMJ Open* 2017; 7: e014018.
25 Shin C, Lee S, Abbott RD, *et al.* Respiratory symptoms and undiagnosed airflow obstruction in middle-aged adults: the Korean Health and Genome Study. *Chest* 2004; 126: 1234–1240.
26 Vinnikov D, Raushanova A, Kyzayeva A, *et al.* Lifetime occupational history, respiratory symptoms and chronic obstructive pulmonary disease: results from a population-based study. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 3025–3034.
27 Souza ECC, Pizzichini MMM, Dias M, *et al.* Body mass index, asthma, and respiratory symptoms: a population-based study. *J Bras Pneumol* 2019; 46: e20190006.
28 Liu Y, Pleasants RA, Croft JB, *et al.* Smoking duration, respiratory symptoms, and COPD in adults aged ⩾45 years with a smoking history. *Int J Chron Obstruct Pulmon Dis* 2015; 10: 1409–1416.
29 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: 159–168.
30 Vogelmeier CF, Criner GJ, Martínez FJ, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Arch Bronconeumol* 2017; 53: 128–149.
31 Miravitlles M, Calle M, Molina J, *et al.* Spanish COPD Guidelines (GesEPOC) 2021: updated Pharmacological treatment of stable COPD. *Arch Bronconeumol* 2022; 58: T69–T81.
32 Miravitlles M, Molina J, Quintano JA, *et al.* Depressive status explains a significant amount of the variance in COPD assessment test (CAT) scores. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 823–831.
33 Soriano JB, Ancochea J, Miravitlles M, *et al.* Recent trends in COPD prevalence in Spain: a repeated cross-sectional survey 1997–2007. *Eur Respir J* 2010; 36: 758–765.
34 Borna E, Nwaru BI, Bjerg A, *et al.* Changes in the prevalence of asthma and respiratory symptoms in western Sweden between 2008 and 2016. *Allergy* 2019; 74: 1703–1715.
35 Mendoza L, de Oca MM, López Varela MV, *et al.* Physical activity levels and associated factors in a Latin American COPD population of patients. The LASSYC study. *COPD* 2021; 18: 393–400.
36 Satia I, Mayhew AJ, Sohel N, *et al.* Language and geographical location influence the incidence of chronic cough in the Canadian Longitudinal Study on Aging. *ERJ Open Res* 2022; 8: 00721-2021.
37 Satia I, Mayhew AJ, Sohel N, *et al.* Prevalence, incidence and characteristics of chronic cough among adults from the Canadian Longitudinal Study on Aging. *ERJ Open Res* 2021; 7: 00160-2021.